THE VALUE OF DIRECT-ACTING ANTIVIRALS FOR THE TREATMENT OF CHRONIC HEPATITIS C IN AN INTEGRATED HEALTHCARE SYSTEM

By
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Abstract:

Problem: Hepatitis C (HCV) affects over 3 million people in the United States. The disease is now curable with new all-oral direct-acting antiviral (DAA) therapies with clinical trial efficacy rates between 90%-100%. However, because the list prices of these drugs are prohibitively high, treatment has not been universally prescribed to all patients with chronic HCV for reasons that vary across payer and healthcare system. This dissertation explores the utilization and value of the new DAAs in the Kaiser Permanente Mid-Atlantic States (KPMAS) health care system by determining predictors of treatment initiation, effects of treatment on resource utilization and cost-effectiveness of different triaging treatment policies.

Methods: The association between patient and provider characteristics and treatment initiation was evaluated with a cox-proportional hazards model. Due to the non-randomized treatment assignment and variations in treatment timing, we created a propensity score matched sample and conducted a time series analysis to assess the effect of treatment of subsequent resource utilization. Cost-effectiveness of triaging treatment approaches was evaluated using a Markov model using probabilistic sensitivity and value of information analyses.

Results: Fibrosis score was not associated with the likelihood of being treated with a DAA. Older patients were more likely to be treated, while those with a history of a substance use disorder were less likely to be treated in our study sample. We did not find any differences in likelihood of treatment across race or insurance type. While we found a downward effect on the rate of post-treatment resource utilization, these effects were not statistically significant. Universal access to treatment, for patients across all fibrosis scores, was the optimal treatment strategy at the $150,000/QALY threshold. Sensitivity analyses showed these results were robust to parameter variations.

Conclusions: KPMAS is providing equitable access to care across characteristics that typically induce disparities, but is uniquely positioned to enhance their linkage to care for some vulnerable patient subgroups. Longer follow-up may demonstrate more significant spillover effects as more advanced disease develops over many years. Expanding access to treatment seems to be the most efficient treatment strategy for chronic HCV from both perspectives.

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Chapter 1: Introduction

Problem Statement:

Hepatitis C virus (HCV) is a chronic condition that leads to substantial physical, mental and economic burden. Since November of 2013, the FDA has approved a series of breakthrough drugs that boast cure rates of over 95% with very few side effects. However, the prohibitively high list prices of these therapies, between $26,000-$150,000 per course of therapy, have caused considerable tension between payers and patients. When faced with such high prices and limited resources, payers and providers have to make difficult decisions regarding treatment. Patients, some who are just learning of their diagnoses, are faced with a possibility of being denied, or delayed, treatment – either because they are not "sick enough" or because they simply cannot afford the drug. While the issue of high drug prices is not unique to Hepatitis C therapies, the infectious nature of the disease and high economic burden of the disease underscore the magnitude of the issues presented by the lack of affordability of these drugs.

Significance of Problem:

Most of the current literature focuses on the previous standard of care – pegylated interferon and oral ribavirin – with substantially lower efficacy and burdensome side effects that in many cases resulted in discontinuation of treatment. As a result, patients remained infected and at risk of transmission. The new all-oral therapies have minimal side effects facilitating adherence. Given how recently these drugs have been approved, it is imperative to understand who is being treated, when and what the potential offsets are. Understanding determinants of treatment with new therapies is critical to ensuring appropriate allocation of resources. While clinical trials have demonstrated cure rates ranging between 95-99%, the real-world effectiveness and subsequent impact of cure remains to be understood in the new DAA era. It is crucial to achieve a better understanding of the magnitude of the value of these therapies and the treatment and payment policies that provide, or impede, access to care. The goal of this research project is to provide payers and physicians with a more nuanced understanding of how patients with Hepatitis C are being treated with 2nd-generation DAAs within the economic constraints that they face.

Brief Overview:

The new second generation of direct-acting antiviral therapies (DAAs), beginning with the release of simeprevir (Olysio, Johnson & Johnson) in late 2013, represent a fundamental transition in treatment. The latest drug, Mavyret (Abbvie), is a pan-genotypic therapy that represents a substantial advancement in the treatment landscape. The American Association for the Study of Liver Diseases and Infectious Diseases Society of America have named DAAs the new standard of care. [1]

While the multiple treatment options have obvious clinical and public health advantages, the high prices manufacturers set for these drugs raise concerns about access and affordability. Despite the availability of increasingly efficacious treatments and renewed treatment guidelines, a small percentage of infected individuals have actually received treatment. [2] Given the high costs of treatment and criteria imposed by payers, providers sometimes prioritize the treatment of certain patients over others although recent studies show that this may increase patient risk of morbidity and mortality. [3] In the new treatment era, in which there are a multitude of options given a patient's clinical profile, this dilemma leads to unanswered questions about who, and when, providers are treating with the new DAAs and the economic and clinical consequences of these decisions.

Multiple clinical trials have demonstrated that these new therapies are curative, with rates of sustained virologic response exceeding 90% in most trials. [4-8] Curing HCV can work to slow down, and potentially reverse, the severe scarring of the liver, which can reduce the risk of cirrhosis, hepatocellular carcinoma and liver transplant. Higher cure rates can potentially decrease HCV-related complications often associated with high medical costs and resource utilization. It has been hypothesized that high levels of effectiveness can reduce future resource utilization and medical costs. However, studies examining cure rates, and subsequent resource use and healthcare costs, in less controlled populations are limited. [9-11]

The public health challenges of identifying or screening undiagnosed cases of HCV and connecting infected individuals to care remain key pieces to the possibility of eradicating chronic Hepatitis C. [12] Screening recommendations put forth by the World Health Organization and the United States Preventive Services Task Force will help to identify those who require treatment. Although these remain important steps in eradicating HCV, this research project will focus on the treatment decision, and its effects, in the cascade of care.

Epidemiology of Hepatitis C:

HCV is an infectious disease that can range in severity from a mild illness lasting a few weeks to a serious, lifelong illness that attacks the liver. The infection can be acute or chronic which is spread primarily through contact with the blood of an infected person. The chronic infection can lead to more severe liver sequelae such as chronic liver disease, cirrhosis or hepatocellular carcinoma. There are between 2.7 and 3.9 million people chronically infected with HCV in the United States, most commonly infected with genotype 1 of the virus. [13] Most individuals infected with HCV develop a chronic infection and of these, 15-20% develop liver cirrhosis, which can result in end-stage liver disease (ESLD) and hepatocellular carcinoma (HCC). HCV is also the leading cause of liver transplants in the United States. [14, 15] Commonly experienced extra-hepatic manifestations of hepatitis C include chronic kidney disease, type 2 diabetes, depression and certain types of lymphoma. [16] The highest prevalence of HCV is among adults aged 40-49 and the aging of this cohort has and will continue to increase the clinical and economic burden of the disease. [17] Greater than 65% of these infections are among the baby boomer population - the greatest prevalence of chronic HCV is in this particular age group. [18] Further, HCV deaths have surpassed deaths from HIV/AIDS. [19]

A model forecasting the incidence of advanced liver disease indicated the proportion of cases with advanced fibrosis was predicted to rise over the next two decades with 25% of the HCV population having cirrhosis in 2010 and rising to 45% in the year 2030. [20] Cirrhosis and liver-related complications were most common in those over the age of 60 – as the HCV population continues to age, the most severe sequelae of chronic HCV will develop. Others have provided evidence that the number of patients with decompensated liver disease is expected to quadruple over the next 10 years and the number with hepatocellular carcinoma is expected to triple. [18, 21]

Recommendations for HCV Screening

Over time, the guidelines for screening for HCV have been revised as evidence continues to develop of the evolving epidemiology of the disease. Despite screening recommendations, about 50-75% of those chronically infected with HCV are unaware of their infection since the disease remains asymptomatic for years. [22] In 2009, the AASLD [23] put out guidelines that patients with specific clinical profiles be screened for HCV infection including,

but not limited to, those who have injected illicit drugs, patients co-infected with HIV, recipients of transfusions or organ transplants prior to 1992 and current sexual partners of HCV-infected partners. [23]

The CDC Division of Viral Hepatitis workgroup developed evidence-based recommendations in 2012 based on 30 observational studies. [24] Based on their findings and an NHANES analysis, the following recommendations were made: patients born between 1945-1965 should receive a 1-time screening for HCV and all those identified with HCV should receive a brief alcohol screening and interventions as clinically indicated.

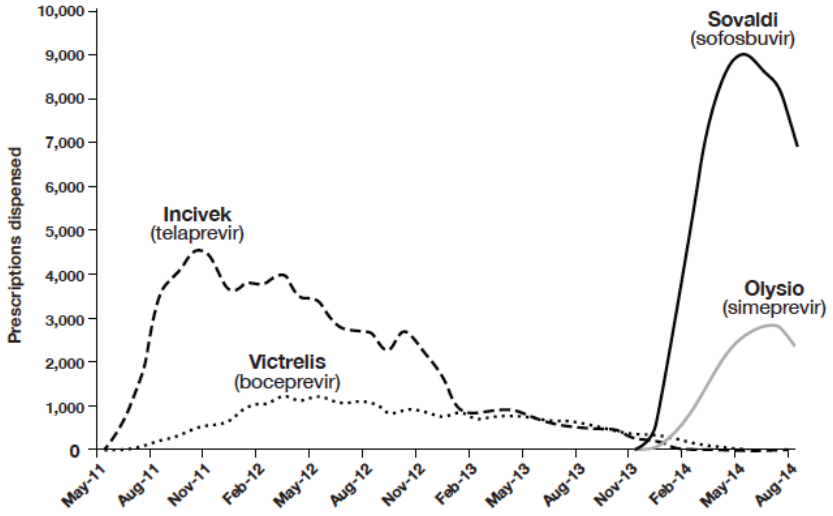
The following year, the United States Preventive Services Task Force issued two Grade B recommendations to screen persons at high risk for infection and a one-time screening to adults born between 1945 and 1965. With the passage of the Affordable Care Act, payers are required to cover these screenings with no patient contributions.

Current patients with HCV were primarily infected by exposures between the 1960s and early 1990s and so 70.1% of the HCV antibody positive patients today were born between 1945-1965. [25] In 2010, the first members of this baby boomer generation became eligible for Medicare and many more continue to become eligible as time goes on. Without appropriate screening, many of these patients infected during this period may be learning of their diagnoses at a much later stage in the disease posing a substantially higher burden on the public insurance program.

Recommendations for HCV Treatment:

The treatment for HCV has evolved over time and the options for treatment continue to grow. The first agent, interferon alpha-2b, was approved by the FDA for the treatment of hepatitis C in 1991. This treatment imposed a great deal of burden on the patient requiring three injections a week for 24-48 weeks and the SVR, or cure, rates were less than 30%. In 1998, interferon was approved in combination with ribavirin for a 48-week treatment course for genotype 1 and 24 weeks for genotype 2. Cure rates increased to 29% for genotype 1 and 60-62% for genotypes 2 and 3. A few years later, pegylated interferon alpha-2b was approved in combination with ribavirin, which improved cure rates further (41% for GT 1 and 82% for GT2-6) and reduced the burden of administration with one dose per week. Pegylated interferon alfa-2a had similar effectiveness with ribavirin. About a decade later, the FDA approved the first of the protease inhibitors – telaprevir and boceprevir. These were often used in combination with interferon and ribavirin.

Beginning in 2013, the medical community saw another major medical breakthrough with the discovery of the direct-acting antiviral therapies. The different combinations of these new DAAs essentially serve to inhibit the replication of the viral HCV RNA throughout this process – this is the novelty of these therapies. [26] These inhibitors are critical to interferon-free regimens given their broad genotype coverage and high barrier to resistance. Given this mechanism of action, these therapies are curative essentially revolutionizing the way we care for these patients. Previously used therapies also provided cure but had much lower rates of efficacy. The significant change in the treatment landscape created by the approval of these new drugs is seen in the figure below [27] where we see the surge in use of sofosbuvir, the first of the second-generation direct-acting antivirals, while the use of the older generation drugs plummeted and eventually found itself removed from the market. The DAAs are also of much shorter duration and are much better tolerated with fewer side effects compared to the non-specific antiviral interferon and ribavirin therapies.



The majority of clinical trials conducted on the second-generation DAAs showed cure rates of over 95%, with or without ribavirin and different prior treatment experience. [28] In 2013, simeprevir and sofosbuvir were the first DAAs approved as a combination therapy to treat patients with chronic HCV. Some patients were treated with these oral drugs in combination with ribavirin based on their unique patient history. A year later, Harvoni (ledipasvir/sofosbuvir) was the first once daily pill approved by the FDA. Many new therapies have received FDA approval over the past few years for patients with and without cirrhosis, both treatment naïve and experienced and different HCV genotypes. In June of 2016, the FDA approved Gilead's Epclusa (sofosbuvir/velpatasvir) – the first

pan-genotypic DAA for the treatment for HCV. This significantly changed the market given the limited therapies available for the more uncommon genotypes of HCV. Abbvie's Mavyret, approved in August of 2017, is also a pan-genotypic therapy, but priced at a WAC of about $26,000 – the lowest of all DAAs currently available thereby changing the market dynamic drastically. Further, Mavyret was the first 8-week therapy to receive FDA approval.

These rapid developments in treatment for HCV can be beneficial only combined with access to appropriate care. Economic and clinical assessments of the impact of these treatments in real-world populations are necessary to evaluate and limit barriers to treatment.

Economics of Hepatitis C:

There is widespread agreement that providing patients with meaningful drug benefits can generate savings in other areas of the health care system. Furthermore, there is also a substantial body of evidence that prescription drugs can reduce the need for other health services such as hospitalizations or emergency departments visits. [29-31] This has been well documented in many chronic conditions. [30, 32-35]

It is imperative to study the effect of DAAs on subsequent resource utilization and associated costs. The primary justification of value for these high prices by the companies that manufacture the drugs is the potential for significant cost savings in the future that can accrue to all stakeholders involved in paying for the drug – patients, payers and health systems. Chronic HCV, if left untreated, eventually progresses to extremely severe stages. The most severe sequelae, like hepatocellular carcinoma or decompensated cirrhosis leading to a liver transplant, are the most burdensome on the system. Other extra-hepatic conditions, that patients with HCV are at a higher risk for, such as chronic kidney disease or end-stage renal disease, are also avoidable complications if HCV is treated. If there is a cure that can stop the progression of liver fibrosis and cure the patient of the virus, then treating the chronic HCV should in theory generate substantial savings in the future thereby demonstrating the value of the drug. While long-term follow-up is ideal for this chronic disease, the short-term observation of these trends can provide initial insight into whether or not these drugs are achieving the value they were proposed to generate.

The economic burden of Hepatitis C, both direct medical costs and resource utilization, is well documented nationally. Researchers have used the National Ambulatory Medical Care Survey [36, 37], the National Hospital Ambulatory Care Survey [36, 37], the Nationwide Inpatient Sample [37, 38] and the National Hospital Discharge Survey [38]

to quantify the magnitude of healthcare resource utilization and have consistently demonstrated that chronic HCV imposes a significant burden on the healthcare system. A diagnosis of HCV is associated with increased resource use and greater healthcare costs. Resource use is highest and continues to increase in the baby boomer generation. [25, 37] Studies consistently report that high costs associated with HCV are largely driven by severe liver sequelae such as decompensated cirrhosis, hepatocellular carcinoma and liver transplant. [39-41] Many studies have found a gradual increase in both all-cause and HCV-related costs, with increasing disease severity. [42]

A recent study examined patients from the Chronic Hepatitis Cohort Study receiving care from one of four integrated healthcare systems. Teshale et al. found that patients with chronic HCV had a hospitalization rate of 27.4 per 100 person-years compared to 7.4 for those without chronic HCV, or a 3.7-fold higher all-cause hospitalization rate than other health system patients. [43] Other studies have found that the cost of HCV sequelae increases with the progression of disease [42, 44] and patients with end-stage liver disease have a 3.3 fold increase in their total adjusted direct healthcare costs [42] when compared to non-cirrhotic patients.

Studies of commercially or self-insured employer populations have examined the resource utilization and costs associated with HCV infection and the same measures associated with treatment using the older generation drug therapies. [11, 42, 45, 46] For example, a study using an employer-based commercial claims database examined resource utilization and cost for HCV patients who were treated with telaprevir or boceprevir – first-generation DAAs, used in combination with interferon and ribavirin, no longer available on the market. [10] These HCV patients experienced high discontinuation rates of therapy –many real-world studies of the utilization of telaprevir and boceprevir found about one-third of their study samples to discontinue therapy [47-49] which in turn can increase resource utilization and costs in the future when treatment for chronic HCV is discontinued. [50, 51] A report by Truven Analytics found that about 40% of patients who initiated HCV treatment with a first-generation therapy were treated for fewer than the recommended minimum duration and subsequently experienced the highest post-treatment total and HCV-specific costs. [52]

It is also important to note that when patients discontinue therapy prematurely, they are at a higher risk of relapse and the likelihood of developing advanced liver disease increases thereby increasing overall healthcare costs and HCV-related costs. [51] The new DAAs have significantly improved adherence rates over the previous standard of care. [53] When patients complete therapy with these new DAAs as recommended, the probability they are cured

substantially increases. Greater ease of administration [2], with all-oral therapies, have clinical and potentially large economic benefits.

A few studies have explored the potential burden of out-of-pocket costs for HCV patients. Karmarkar et al. used administrative pharmacy claims data to quantify initial therapy abandonment for sofosbuvir as a function of out-of-pocket costs. Out-of-pocket (OOP) costs ranged from $0 to greater than $10,000 for the initial prescription. Adjusted rates of abandonment were significant, in comparison to the lowest OOP category, if members faced costs of $2500 or greater. [54] Yao et al. explored trends in DAA utilization with the introduction of the new medications and their associations with OOP costs in a large administrative claims database. The median OOP costs for those receiving new DAA regimens was comparatively low ranging from $112 to $340, however there was a substantial amount of variation across regimens and the mean costs were high ($1982-$2127). [55] While some patients paid no OOP costs, other HCV patients faced costs as high as $75,831 for the entire regimen. Some manufacturers offer patient assistance programs, including drug coupons, which can offset some, or all, of the OOP costs patients face in filling DAA prescriptions. We do not explore the relationship between cost and adherence in this study, but it highlights a policy issue– the most efficient way to make necessary medications available to patients.

Insurer Burden

Insurers are facing difficulties providing coverage for the multiple high cost prescription drugs currently on the market – the DAAs being just one of them. [56-58] Payers are looking for certain tangible metrics that demonstrate the real-world effectiveness of these drugs in order to expand coverage – demonstrated adherence and achievement of a sustained virologic response similar to those found in clinical trials. Observational studies in various patient populations to demonstrate effectiveness can provide evidence of value to payers and systems determining how to adequately and efficiently utilize the new DAAs. This evidence could encourage payers to expand coverage for more patients. On the supply side, the multiple DAAs on the market can generate competition creating more opportunities for payers to lower their costs. [58] Recent studies have documented insurance type as a significant factor in determining DAA approval or access for HCV-infected patients. [59-61] Disparities in access to therapy in the Medicaid population, for example, highlight the issues of affordability facing the poorest amongst the infected population. [59]

Public Payers:

Studies reveal that a disproportionate share of HCV diagnoses is found amongst individuals covered by public insurance. State Medicaid programs cover the nations poorest individuals and the federal Medicare program is unable to negotiate prescription drug prices. Although many of these Part D programs are outsourced to private payers, Medicare is currently still left paying 80% of the cost of the drug placing an increasing strain on the budget.

Menzin et al. found that HCV-infected individuals in Florida's Medicaid program with advanced liver disease had greater resource utilization and greater per-patient-per-month costs indicating a need for access to treatment in earlier stages of the infection. [39] Liao and Fischer showed that the proportion of sofosbuvir prescriptions for HCV in 2014 ranged from 2% in Texas to 44% in Hawaii and total spending on sofosbuvir, reported by CMS, was over $1.3 billion in 2014. [62] States that expanded Medicaid coverage spent more of their prescription drug budget on sofosbuvir than those that did not. [62]

Many state Medicaid programs initially outlined restrictions for the reimbursement of sofosbuvir. [63] Some states had implemented disease severity, sobriety and prescriber requirements for coverage of this DAA – denying coverage for the drug if only mild fibrosis could be demonstrated, for example. Many Medicaid programs, including Florida, New York, Delaware, Washington and Massachusetts, have lifted their restrictions as a result of lawsuits. [64]

Kapadia et al. show trends in utilization since the approval of Harvoni over time as states lifted these restrictions. Those states that lifted fibrosis or abstinence restrictions saw the greatest increases in DAA prescriptions over time than those that maintained their restrictive coverage policies. [65] Younossi et al. modeled the clinical and economic impact of an "all-patient strategy" on state Medicaid programs and found that treating all Medicaid patients with Harvoni (ledipasvir/sofosbuvir) resulted in about $3.8 billion in savings. This strategy also resulted in a greater percentage of patients achieving a sustained virologic response and fewer cases of advanced liver disease. [66]

A recent study examined the burden of Hepatitis C to the Medicare system in 2009, immediately prior to the first cohort of the baby boomer generation becoming eligible, and found the economic burden was significant and expected to increase over time as patients continue to age into eligibility. In 2009, Medicare paid $.7 billion in incremental costs for HCV and the treatment of decompensated cirrhosis, the most severe state prior to liver transplant, accounted for about 64% of Medicare's HCV expenditures. [25] As older patients learn of their diagnoses,

given the new USPSTF recommendations, more patients will require treatment creating a greater burden on the public payer. A more recent study explored the current prescription drug benefit designs for chronic HCV drugs available to Medicare beneficiaries. [57] As of July 2015, all Medicare Part D drug plans covered at least one of the newly approved DAAs. Jung et al. found almost all of these plans have high coinsurance and required some type of prior authorization before covering the prescription. Those beneficiaries without any subsidies faced a significant mean out-of-pocket cost for one treatment course ranging from $6297 to $10889. [57]

Private Payers:

Many studies have explored the cost of chronic HCV patients in commercial claims databases to better understand the burden on private payers. Although different payers cover different patient populations, they all came to a similar conclusion that HCV patients have large direct healthcare costs and per-member-per-month costs increase with the severity of liver disease. [42, 67, 68]

Private payers, although covering a different type of beneficiary, have not escaped the difficult decisions presented by the prices of these new therapies. For example, major pharmacy benefits manager (PBM) Express Scripts dropped Gilead's Harvoni from its preferred formulary and exclusively covers Abbvie's Viekira Pak. [69] While the PBM has leveraged its negotiating power on behalf of its beneficiaries, it has also limited consumer and prescriber choice to some extent. Other private payers have put in place prior authorizations that result in immediate denials or delayed approvals for medication.

Many private payers have also now begun to reverse their restrictive coverage policies under the threat of lawsuits. [70] For example, Anthem Blue Cross and Blue Shield plans in 14 states have began authorizing treatment to people in "all stages of fibrosis" at the end of 2015. [64] Moreno et al. found that private payers experienced reduced expenditures over the 3-to-5 year time horizon and experienced overall savings of $10-$14 billion over a 20-year period. [71] Additionally, by increasing coverage, they create spillover benefits to the Medicare program. When patients are treated earlier, before they age into Medicare, the economic burden is substantially reduced. This study highlights a tension unique to the U.S. system - private payers might be hesitant to cover treatment for patients today because Medicare would see the savings in the future. [71]

Predictors of and Time to Treatment:

Previously studied factors, associated with treatment, include patient characteristics, immunologic factors and genetic factors. [72-74] Commonly documented characteristics are HCV genotype, patient treatment history, patient race, comorbid conditions, HIV/HBV co-infection, severity of liver fibrosis and alcohol and injection drug use.

We need an updated, understanding of when HCV patients are being treated with the new DAA therapies. Only one recent study has explored the impact of different characteristics on the receipt of treatment with new DAA therapies in the national veterans population – black patients and younger women were found to have significantly lower probability of treatment. [75] Insurer member populations, with chronic HCV, vary in disease severity, presence of comorbidities, socioeconomic and demographic characteristics. Health systems can better manage their HCV populations if they have insight into other factors that are associated with treatment. Another study, in a large administrative claims database found significant differences in predicted probabilities of treatment between the pre-DAA and post-DAA era, their study ended in 2014 with the approval of Harvoni. [55]

Real-World Effectiveness of DAAs:

Studies on utilization and real-world effectiveness of the drugs are limited given the recency of drug development and gradual shift in provider practice. Published effectiveness studies examine short-term outcomes such as the sustained virological response (SVR), metric of cure according to AASLD/ISDA [3], as was used in clinical trials for the drugs. In many of these controlled settings, patient rates of SVR exceeded 90%. [76-79] Clinical trials have often limited enrollment to patients based on previous treatment success or failure, whether or not a patient has developed cirrhosis, HCV genotype, development of hepatocellular carcinoma, previous use of ribavirin, the first-generation DAA or HIV co-infection. In routine practice, providers encounter chronic HCV patients with heterogeneous profiles and exhibit many of these patient characteristics that indicate a certain treatment. [4-8, 78, 80-84]

Cure rates can vary in real-world practice [85], however, recently published studies on all-oral regimens demonstrate optimistic findings. Two studies examining safety and effectiveness of a treatment regimen including simeprevir and sofosbuvir each found cure rates of 80%. [86, 87] Crude SVR rates varied with patient cirrhosis status, prior treatment experience and HCV genotype. Backus et al. used the Veterans Affairs Clinical Case Registry for HCV and found that overall, rates of SVR were much lower for four different treatment/patient populations and

ranged from 55.6% to 81.6%. [88-90] Treatment naïve patients had higher cure rates than treatment-experienced patients. Patient characteristics such as stage of fibrosis, genetic markers, BMI and prior treatment experience were significant [90] and warrant further exploration in other health care settings with diverse populations.

Younossi et al. examined real-world SVR rates for the all-oral, peginterferon-free and ribavirin-free ledipasvir/sofosbuvir (Harvoni) regimen. After 12 weeks of therapy, researchers found similar rates of SVR, 94%-98%, to the pivotal ION-1 and ION-3 clinical trials for this particular treatment regimen. [91] Even after stratifying the analysis by cirrhosis status, effectiveness remained similarly high. Another group of researchers estimated the effectiveness of a Harvoni regimen in a sample of treatment-naïve veteran population. Of the patients on a ribavirin-free regimen, 91.3% achieved cure while 92% of patients on a Harvoni regimen plus ribavirin achieved cure. Further, patients without cirrhosis who completed 8 weeks of therapy had SVR rates of 93.2% and 96.6% for those who completed 12 weeks of therapy. [92] Walker et al. have examined the same question of effectiveness, in a commercially insured population, comparing Viekira Pak and Harvoni. Unadjusted SVR rates were 98% and 96% for 3D and SOF/LDV, respectively, in a treatment-naive population. Cure rates in these studies were similarly high to those obtained in the clinical trial setting. [1]

Cost-Effectiveness of Direct-Acting Antivirals:

While studies have demonstrated unprecedented cure rates for these drugs, the high list prices set by the pharmaceutical manufacturers have motivated a quest for a measure of value, or efficiency, of these drugs. Cost-effectiveness analysis uses a cost per outcome metric to demonstrate the value of a treatment or medical practice. Although not required as part of the drug approval process in the United States, many have undertaken these studies for the multitude of available DAAs to demonstrate their clinical and economic value. [93] The majority of these analyses have examined the value of these new therapies from the payer perspective as they face a substantial cost when covering numerous beneficiaries with varying clinical profiles. [94-98]

Studies have shown the cost-effectiveness of DAAs in varying treatment scenarios such as delaying treatment [99, 100] for mildly ill patients or treating different percentages of populations. [94] Van Nuys et al. found that treating all patients could generate between $619-$1,221 billion additional QALYs in addition to $139 billion in saved medical expenditures, however the upfront costs of treatment would be more than $150 billion. Others have

found that for lower willingness-to-pay (WTP) thresholds, sofosbuvir-based regimens would only be cost-effective for patients with advanced liver disease, while ICERs for treating most patients, regardless of severity of disease, would be much higher and at times exceed commonly accepted WTP thresholds in the United States. [96, 98]

While Chhatwal et al. concluded cost-effectiveness of sofosbuvir-ledipasvir in limited, specific patient populations, Younossi et al. found this therapy to be more favorable for all patients, regardless of treatment experience and disease severity, also from a payer perspective. All analyses concluded results were most sensitive to drug costs. [94-96, 98] Chahal et al. focused only on patients with HCV genotype 1 and found that treating patients in all fibrosis stages in comparison to those in the latest stages is cost-effective. Further, initiating treatment earlier versus delaying treatment for patients until later stages is cost-effective but some ICERs exceed common WTP thresholds, once again, yielding large aggregate upfront costs. These studies did not include indirect costs, such as loss of productivity, which has been demonstrated to improve when patients achieve an SVR. [101-103]

Labor market productivity [104] and other associated indirect costs of treating HCV, such as informal caregiver time, are necessary to understand the possible long-term cost-savings to society. Additionally, chronic hepatitis C has been associated with multiple other extra-hepatic manifestations such as diabetes, cardiovascular disease and renal dysfunction. [16] The most common liver-related complications often resulting from a chronic Hepatitis C infection include decompensated cirrhosis, end-stage liver disease, chronic kidney disease and hepatocellular carcinoma. These severe complications often result in the greatest physical and economic burden to patients with HCV and may be preventable with the achievement of cure, or sustained virologic response.

Systematic reviews of cost-effectiveness analyses comparing different DAA regimens, with varying treatment duration and patient profiles, demonstrate that the value of these therapies differs depending on the patient population examined. [105-107] Authors found that moving forward, economic evaluations should consider indirect economic benefits and costs, as well as real-world effectiveness data. More studies in different real-world patient populations, healthcare settings and insurance coverage scenarios are also necessary.

Is Prioritizing Treatment the Answer?

Given the economic burden associated with the utilization of these new direct-acting antiviral therapies as highlighted by the dilemmas all payers and providers face, it is important to assess or quantify the value of such

treatment practices. If patients diagnosed with HCV have to wait for treatment until they have developed further complications, despite the AASLD guidelines to the contrary, we must be able to demonstrate an argument for efficiency to the multiple stakeholders involved in this decision-making process.

A recent cost-effectiveness analysis from the UK payer perspective examined the influence of a patient's likelihood of progressing to end-stage liver disease (ESLD) on the value of a cure, or sustained virologic response. [108] Targeting treatment to patients most likely to progress to ESLD is one way to prioritize treatment for HCV while achieving the most efficient allocation of resources. HCV patients in similar stages of fibrosis can progress to ESLD at different rates based on specific prognostic factors. Ward et al. incorporated this heterogeneity into their cost-effectiveness analysis to quantify the value of a cure as a function of time to ESLD when treatment is first initiated. They found that over a 10-year period following the incidence of ESLD, an average patient would accumulate a total cost of 51,105 associated with managing ESLD complications attributable to the management of chronic HCV, decompensated cirrhosis, hepatocellular carcinoma and liver transplant. [108] Further, they found that the financial value resulting from SVR and avoidance of these ESLD complications was estimated to increase as the period between treatment and ESLD onset decreased. [108] The closer a patient was to developing ESLD, the higher the value of achieving a cure.

Chidi et al. examined the value of prioritization implemented from a payer perspective. [109] They evaluated the cost-effectiveness of current Medicaid policies compared to unrestricted access to HCV treatment for all patients and the long-term impact on the Medicare budget. From the Medicare perspective, the authors found that an unrestricted strategy was cost saving and more effective compared with current Medicaid coverage policies. [109] The full access strategy was more cost saving for younger cohorts from the CMS perspective. This is expected as the younger the HCV patient is, the more likely it is that advanced liver complications will be avoided before patients age into Medicare eligibility – accruing long-term cost savings to both payers.

Chattwal et al. highlighted in their review that previous estimates of cost-effectiveness may be underestimated given that these extra-hepatic consequences were not included in the calculation. [106] A recent study by Leidner et al. explored the impact on the cost-effectiveness of early HCV treatment given potential reductions in non-hepatic mortality. [110] Leidner et al. constructed a state-transition model to determine the effects of reductions in non-hepatic mortality varying from no effect to a 100% reduction. They found that when they included a 44%

reduction in non-hepatic mortality, the ICER fell by 76% from $314,100 to $76,900 for patients with no fibrosis and by 43% from $62,500 to $35,800 for patients with moderate fibrosis. [110] This study demonstrates spillover effects such as reductions in all-cause mortality.

There remains a substantial amount of uncertainty over the long-term effects of these DAAs and the long-term outcomes for specific patient populations. Value of information analyses can provide some insight into what parameters or variables require more research that can support for targeted treatment practices in the face of continued budget constraints.

Gaps in the Literature:

Given the recency of the development and marketing of the 2nd-generation DAAs, minimal work has been done in the health services research space around the utilization and effects of these drugs.

Previous studies have explored predictors of therapy including patient demographics, clinical histories, and socioeconomic variables. The variables that describe a patient's clinical characteristics continue to be relevant as progression of disease, biologically, has not changed with the approval of new therapies. However, now financial and system factors may play a role given the burdensome price of the new drugs. We found only one other study that examined the association between race, gender and treatment in the VA population. [75] The VA population is unique due to the clinical profiles of these patients, their insurance coverage, the discounts on the drug prices the VA secures, and the general health system infrastructure. Given the fragmented nature of our health care system and the fact that patients receive care in many different settings, we aim to begin to fill this gap, in Aim 1 of this thesis, by understanding predictors of treatment in one sample of chronic HCV patients in an integrated healthcare system.

Parties responsible for paying for these drugs are in a difficult situation – the patients they care for are not just patients chronically infected with HCV. They must allocate resources to a diverse patient population given budget constraints. The high list prices of the DAAs make it difficult to do this. This sometimes leads to selective coverage of these drugs. These kinds of studies can explore if patients are more or less likely to be treated for reasons that contradict clinical guidelines. The results can provide some actionable information that providers and systems can use to implement policies that can better link patients to treatment. If we find that financial variables [59, 61] are serving as barriers to care, this also helps to pinpoint policy changes that can be made to make DAAs more

affordable. For example, Do et al. found, in one particular health system, that one in four patients are initially denied access to sofosbuvir/ledipasvir (Harvoni) upon initial prescription of medication. [111] Although these patients are eventually approved through appeal, this delays the initiating of treatment and subsequently cure. [1]

Another major gap in the literature is the effect of the new DAAs on economic outcomes such as healthcare resource utilization. A justification of the value of these drugs is the potential for long-term savings with resource offsets. Most of the studies that have answered these questions have focused on the previous standard of care. [112-115] The results of these studies are promising in that they show not only do interferon-based therapies show some downstream reductions in utilization over no treatment, the first-generation therapies, subsequently showed even more downstream reductions in economic outcomes over time. The new DAAs have demonstrated cure rates of over 95% while ranging between 50-75% in the old therapies. [28] If we see significant differences due to treatment with first-generation drugs, we can expect to see greater downstream savings with a cure. Cost-effectiveness analyses of these drugs find the investment in treatment yields a substantial amount of downstream savings. [101, 105, 109, 110, 116, 117]

With the approval of the new drugs happening only during the past few years, there is a natural lag in the ability to study any spillover effects of these drugs. Some cases studies have been published that demonstrate reductions in hospital admissions and healthcare costs for even the most complex cases of chronic HCV. [118] While these are excellent real-world examples of HCV patients, studies on a much larger scale will prove beneficial in demonstrating the long-term value of treating patients today. In order to determine if there is a similar effect in the new drugs, we need years of follow-up during which we can capture the prevention of the most burdensome sequelae of chronic HCV – liver cancer, chronic kidney disease, decompensated cirrhosis and liver transplants. Aim 2 of this study is a first step in filling this gap in the literature.

While the cost-effectiveness analysis literature has grown rapidly [95, 96, 100, 109] in light of the prices of these new drugs, we hope to fill a few key gaps in the literature in Aim 3 of this study. Previous studies have explored the value of triaging policies explicitly from the CMS perspective and the VA perspective. We plan to use some key health system-specific parameters, including the distribution of HCV patients across the disease spectrum and the real-world effectiveness, or cure rate, in the study sample from the KPMAS HCV registry. We also plan to conduct our study from both the societal and health care sector perspective. We will aim to estimate and incorporate indirect costs, including loss of productivity and costs of informal caregiver time, to better approximate the value from a

societal perspective. We will also take the probabilistic sensitivity analyses one step further than what is found in the current literature by conducting value of information analyses (VOI). Given the uncertainty of how the disease manifests in each patient, and subsequent uncertainty in the magnitude of necessary healthcare resources, it may be beneficial to conduct further research around these model parameters. VOIs can help quantify this investment in future research in order to increase the certainty with which we make treatment strategy recommendations.

Dissertation Organization

This thesis contributes to the growing literature by examining these issues in one health system but can provide a framework for continued exploration in other patient populations and settings.

The dissertation is organized into three empirical papers and a concluding chapter. Chapter Two examines the association between patient, clinical and healthcare characteristics associated with time to treatment initiation with direct-acting antivirals for chronic Hepatitis C. Chapter Three explores the potential spillover effects of direct acting antiviral therapies in the form of resource offsets. Chapter Four assesses the value of various restrictive and expanded treatment policies for Hepatitis C. Chapter Five summarizes our contributions to the field, the policy implications of our results and future research considerations.

Aim 1: Characteristics Associated with Time-to-Treatment Initiation for Chronic Hepatitis C with Second Generation Direct Acting Antivirals

Introduction:

With the entry of the new direct-acting antivirals (DAA) onto the market, patients are often treated at different points along the course of chronic Hepatitis C (HCV). Budget constraints may motivate these efforts to temper healthcare expenditures. Given that the American Association for the Study of Liver Diseases (AASLD) recommends treatment for all HCV patients, it is critical to understand what factors may be driving the decision to initiate therapy in some patients over others. We use a time-to-event analysis to understand what types of patients are more, or less, likely to be treated in an integrated health care system.

Understanding these associations can help providers and systems determine if patients are being linked to care appropriately and efficiently. Any significant relationships found in this analysis will provide actionable evidence of areas where the health system can improve their mechanism for connecting patients to and following them through successful treatment. Lack of significance indicates signs of equitable delivery of care. Patient demographic characteristics include age, gender, race and insurance status. Fibrosis score, as a metric of disease severity, was the primary variable of interest given the triaging treatment practices currently in place. We also included a number of clinical comorbidities that may complicate liver disease and therefore influence the decision to initiate DAA treatment. We included extra-hepatic manifestations such as chronic kidney disease that may lead to end stage renal disease. These conditions can complicate the management of HCV or can be signs of advanced liver disease. We also studied the association with provider factors like location of service.

While treatment completion and efficacy rates for these drugs are exceptionally high in the controlled settings of clinical trials, we aim to measure persistence and effectiveness in this real-world setting. Any differences in persistence or cure by patient characteristics may further pinpoint underlying reasons for physician treatment decisions about DAA therapies.

Conceptual Framework:

While clinical factors may motivate a provider's decision to initiate prescription drug therapy, other factors may also play a key role in determining the appropriate course of treatment for a given patient. Lipton and Bird first proposed a model to provide a framework within which to understand and assess the strength of these influences on a physician's prescribing practice. [119] The objective of this analysis is to understand potential predictors of treatment initiation among patients with chronic HCV. With the approval of the new curative therapies and the screening recommendations laid out by the Centers for Disease Control and Prevention (CDC) and the United States Preventive Services Task Force (USPSTF), it is critically important to understand treatment patterns in such a diverse patient population facing a substantial change in the treatment landscape. [1, 120] This is a significant gap in the literature since we know that all patients who are diagnosed with chronic HCV are not receiving treatment. [59] Aim 1 examines how patient and provider characteristics interact, within a system, to determine HCV treatment.

The system factors create the environment in which clinical decision-making occurs. Many of these system factors construct the boundaries within which providers must practice and therefore influence prescribing decisions. For example, the providers in this study are subject to the healthcare policies set up by Kaiser Permanente Mid-Atlantic States (KPMAS). These include the drug formularies that indicate which of the DAAs are preferred, the way in which care is coordinated within the system and how provider practices are set up within KPMAS. Providers may also take into consideration treatment guidelines outlined by national societies such as the AASLD. Although providers are encouraged to follow these guidelines, the environment in which they practice and the types of patients they see may steer them onto an alternate treatment route.

While the system sets up the boundaries of this environment, provider and patient characteristics within and across systems lead to variation in prescribing practices. Specifically, providers are subject to the system-level policies but may vary in practice due to the particular patient they are treating. For example, while the AASLD treatment guidelines and practice organization within KPMAS may recommend a certain path of care for an HCV patient, the provider takes into consideration the unique situation of each patient in order to make a treatment decision that is most appropriate. Severity of liver disease, existence of comorbid conditions or a history of other conditions all factor into a physician's decision to treat a patient with DAAs. Provider experience with a disease and specialty of practice can also influence how they choose to treat patients and at times may deviate from treatment

guidelines. Given the recent constraints placed on payers and systems by the price of the DAAs, perceptions about a patient's ability to afford or adhere to the medication regimen may also be a factor given that the drug is curative and the disease is infectious. While we do not have measures of these perceptions in our study, they are critical to the discussion about the new DAAs.

Data:

We used both administrative claims and electronic health records (EHR) from KPMAS to conduct this study. KPMAS is an integrated healthcare system that serves over 700,000 individuals in Maryland, Virginia and the District of Columbia. KPMAS includes both private and public insurance programs. The demographics of KPMAS' enrollees closely match those of the population it serves. As of January 2017, the population demographics were the following: 53% female, 40% non-Hispanic Black, 35% non-Hispanic White, 12% Hispanic and 10% Asian/Pacific Islander. The KPMAS data repository available will include 100% of administrative claims and greater than 90% of all patient prescriptions. Laboratory/diagnostic results, outpatient visits, urgent care visits and procedures are captured in an electronic health record.

KPMAS' EHR system, KP HealthConnect, provides patients and providers an opportunity to coordinate care. It links important information regarding provider visits or hospitalizations, lab test results, prescription fills and billing information. Both members and physicians can access these records – the integration of all this information into one electronic record makes this a great tool for both members and providers. KP HealthConnect was the source of all of our patient-level clinical data for this analysis. We pulled patient demographic information, patients' clinical histories, lab test results, procedure results, and insurance information and prescription records. Dates of diagnosis, enrollment in the Kaiser Permanente health plan, and treatment were all extracted to use in the construction of the study cohort and outcome variables.

KPMAS has an established HCV Registry, which identifies current and historic patients with HCV using hierarchical criteria (Figure 1). The most specific criteria is that of HCV RNA, which accounts for >60% of the registry. This registry allowed us to identify the population of interest and gather data to observe patients with chronic HCV over the course of the disease and treatment process.

Study Cohort:

The study period began on November 1, 2013. This date marked the introduction of second-generation DAA therapy, Sofosbuvir, to the United States market. We followed HCV patients who had not yet been treated with any DAAs as of November 1, 2013 and who still had a confirmed diagnosis of HCV, as well as patients who were identified with HCV after that date. In this second-generation era, patients could be treated with a therapy regimen using sofosbuvir (Sovaldi), simeprevir (Olysio) or ledipasvir (Harvoni).

We considered clinical and plan data in constructing the study cohort for this analysis given the date of the release of the first DAA. Patients had to meet a certain set of clinical criteria to be confirmed a chronic HCV patient in the KPMAS registry and we used the same criteria here (Table 1). Once the patient met these laboratory and prescription criteria, we excluded patients who had not been enrolled continuously for 12 months prior to study start date of November 1, 2013. We allowed for a 45-day gap in coverage to account for lapses due to plan changes. If there was a larger gap in coverage, we would not be able to adequately capture the baseline measurements for our study – if a patient had an alternative form of coverage while out of the KP health plan, we would not be able to capture this resource use or their clinical characteristics during this time period. We had access to longitudinal data on patients through May 31, 2016.

We also had access to the date of death, the date of enrollment in the Kaiser Permanente health plan and if applicable, the end of a patient's enrollment in the Kaiser Permanente health plan. Death data was informed by the electronic medical record and from the social security index (SSI).

The survival analysis required a clear definition of three components and they are outlined below within the context of our study.

Origin:

Our study cohort included both *incident* and *prevalent* cases – those diagnosed during the study period and those who have been diagnosed previously and have been followed in the registry prior to November 1, 2013. To study time-to-treatment for a disease, we need the date of diagnosis, however, a person may have been diagnosed many years before the study period start, resulting in lead-time bias. It would artificially increase the time it took for a prevalent case to be treated since the new DAA therapies were not available for use until 11/1/2013. Further, we

wanted to understand factors associated with treatment in the new DAA era, after 11/1/2013, to ensure patients had a non-zero probability of being treated with one of these drugs. The baseline date for prevalent HCV patients was therefore truncated at 11/1/2013 and the baseline date for incident HCV cases was the date of confirmed diagnosis as found in the health record.

Definition of Events:

Patients experienced one of four events during the study period. Patients were treated at some point between 11/1/2013 and 5/31/2016. In the survival analysis, treatment constitutes a "failure" or having the "event" of interest. We used a regimen start date based on the first prescription fill for a patient to determine treatment initiation. Further, while there are multiple DAA regimens that can be prescribed, we considered the initiation of any regimen as a patient being treated since the study period was short in comparison to the natural progression of HCV. Patients could experience death at some point before having received treatment or the end of follow-up and these would be censored observations due to loss of follow-up. Death dates were confirmed using the death records and the social security index. Patients' enrollment period from KP could also end during the study. We used administrative records from the KP Health Plan to determine enrollment dates. Finally, patients could be followed through to the end of the study period and would be administratively censored, or right-censored.

Dates:

We had exact dates for each of the events or diagnoses of interest in the database. Specifically, we had date of birth, date of diagnosis, the date of the first treatment regimen start, the date of death if a patient died over the course of the study period and the dates of health plan enrollment and disenrollment. We also had the exact result dates for each of the different tests used to diagnose and assess liver fibrosis.

Given that a large proportion of our study sample has been a part of the registry for many years, with a diagnosis date before the beginning of the study, many patients have a series of test results prior to the study start date. We limited test results to those that occurred on or after the baseline date for each patient. Specifically, we allowed for a two week buffer prior to the baseline date to account for time between the date the test was performed and the results ready for review by the physician.

Primary Independent Variable:

The primary variable of interest was the clinical measure mostly commonly used for assessing severity of chronic HCV [121] – a fibrosis, or 'F', score. These scores can be determined by either of the tests described here. The vibration controlled transient elastography is less invasive and has recently become the standard method of assessment. This ultrasound-based technology [122] assesses "the images of an acoustic wave generated by a sound source" as it passes through the liver – the resulting score in KiloPascals is then converted to an F-score on a scale of 0-4. [121] Zero indicates no liver fibrosis and 4 indicates the patient has developed liver cirrhosis. The Fib-4 is calculated using the results of liver enzyme tests (platelet levels, aspartate aminotransferase (AST) and alanine aminotransferase (ALT)) and patient age. [121] We then converted this score to one on the F-score scale; however, the exact cut-offs for this conversion can vary. There is much more clarity around the significance of Fib-4 values at the lower and upper ends of the range of scores and how they can be mapped onto the F-score range. Specifically, at KPMAS, physicians conclude that patients have minimal fibrosis, or F-scores between zero and one, if the Fib-4 score is <1.45 and have advanced fibrosis or are cirrhotic above Fib-4 scores of 3.25. [123] There is less clarity regarding the scores between 1.45 and 3.25 and how well they map onto the F-score scale. Therefore, patients below a Fib-4 score of 1.45 were assigned an F-score of 0-1, those between 1.45 and 3.25 were assigned an F-score of 2, and those in the upper interval were assigned a score of 3 or 4. [123] Given this uncertainty, we regrouped the F-scores into the following three categories: 0-1, 2 and 3-4 or mild, moderate or advanced fibrosis.

There was a substantial amount of variability in the number of F-scores a patient had over the course of the study period. Even more importantly, the Fibroscan diagnostic procedure became a standard procedure for assessing liver fibrosis at KPMAS in March of 2015 and so only a subset of the study sample had F-scores derived from a Fibroscan during our study period. The majority of the study sample had at least one relevant Fib-4 score. We observed a wide range of the number of test results for each patient by limiting the test results to the specific baseline date intervals.

Out of a total of 2962 patients that met our criteria, 2248 had an F-score that met our criteria for baseline fibrosis measurement. About 18% of these baseline scores were determined by a Fibroscan measurement and out of all time-varying F-scores, only 15% were based on a Fibroscan. There were 265 patients diagnosed after March 2015 of which only 36 patients had multiple Fibroscan measurements. While this may have changed since the

Fibroscan was incorporated into the standard diagnostic process at KPMAS, majority of patients in our study sample only had one Fibroscan.

We defined a "baseline F-score" for each patient using a hierarchy of preference for scores. We first limited the choice of baseline scores to those that fell between the baseline minimum dates – 12 months prior to the baseline date – and baseline maximum date – two weeks after the baseline date to provide a buffer for any short gaps in coverage. If patients had a Fibroscan during that period, that was designated the baseline F-score. If patients only had Fib-4 test results during that period, we limited the choice set to those that had conducted the liver enzyme tests on the same date. If patients did not have a Fib-4 score with all three tests on the same date, we picked the Fib-4 score for which the three lab tests had been conducted within 90 days of each other.

While patients may not have had a baseline F-score as our criteria required, they might have had F-scores after this baseline period. Further, some patients may not have had any scores that fell within our study period.

Given that we had multiple F-scores for patients over the course of the study period, we allowed F-score to vary over time in the cox proportional hazards model. Patients are not all treated at the same time and so it is possible that changes in this measure of disease severity could change the likelihood of treatment initiation over the course of the study period. Severity of disease is a primary factor in deciding a course of treatment for patients across all clinical contexts. In the case of chronic HCV, the greater policy issues surrounding affordability of the new DAA therapies further enhance this influence. With such high prices, payers, providers and systems are, to varying extents, using this clinical metric to determine who does and does not receive immediate treatment. Some healthcare systems also strongly recommend treatment for patients above a certain F-score while continuous monitoring for patients below that threshold – including KPMAS. We examined the extent to which this was occurring using the distribution of F-scores across treatment status.

Covariates:

We also included other clinical characteristics in our analysis to assess their relationship with treatment. There are many clinical conditions or comorbidities that can influence the progression of liver disease in HCV patients. The magnitude of the effect of these clinical conditions varies and differs by study population. The

literature is mixed – while some conditions can hasten the progression to more severe liver disease, others have been found to be protective.

The primary demographic covariates included in the analysis were gender, race and age. KPMAS provides reported and imputed data on its members' racial, geographic and socioeconomic characteristics. This resource allowed for more complete data on important characteristics of the patients in our study cohort. Gender was a categorical variable and indicated either male or female and age was a continuous variable operationalized as the age-at-entry of the study. Race was self-reported and categorized as: Asian-Pacific Islander, Black, Hispanic, Multiracial and/or White.

Geographic characteristics included state of residence and healthcare service area. State of patient residence included Maryland, Virginia or Washington D.C. Service area indicated where patients were receiving care from their primary care physician. The service area is suggestive of a proxy for a patient's medical home. This information is also of particular importance when comparing patients covered under Medicaid since the reimbursement rules differ across states for certain HCV drugs. Service area includes the Baltimore area, District of Columbia/Southern Maryland and Northern Virginia.

Insurance type was also a categorical variable: commercial, Medicare, Medicaid, dual-eligible and other. The original data from the health records indicated if a patient had any one of these types of insurance coverage at any time during the study period. Multiple payers covered some patients over the course of the two and a half year study period. We narrowed the categories down to the four types of payers by indicating how certain payers take precedence over others. Specifically, if a patient had Medicare at any time, they were classified as having Medicare. If a patient had Medicaid at any time, they were classified as having Medicaid. If a patient had Medicare and Medicaid, they were categorized as dual eligibles as this is a unique population.

We also collected information on HCV genotype (GT 1 – GT 6). It is important to identify a patient's HCV genotype as DAA regimens are genotype specific.

Comorbidities

The comorbidities were identified using a combination of diagnosis, medication and laboratory data. We were interested in knowing and including in our analysis whether or not the patient had a history of a certain

condition or already had a confirmed diagnosis of a specific condition at baseline. We define baseline as having the specific diagnosis or procedure code prior to the two-week buffer before the baseline date (baseline minimum date). Stroke, congestive heart failure, depression, hypertension, myocardial infarction and liver cancer were all identified using their diagnosis codes prior to the baseline minimum date. KPMAS uses medication data to identify diabetes status, HBsAG and HBV DNA results to identify hepatitis B co-infection, and EHR transplant dates to identify patients who have had a prior liver transplant. Smoking is identified via self-report at KPMAS and baseline status was defined as either smokers as of the baseline date or no history of smoking. Patients were either identified as being treatment experienced or treatment naïve and this was determined using prescription records and medication codes prior to the baseline minimum date. Treatment history has been discussed in the literature as impacting treatment success or treatment initiation. [124, 125]

We also had diagnosis data on liver-related complications. Patients could develop decompensated cirrhosis or end stage liver disease prior to the baseline minimum date, post the baseline period or during the baseline period. The presence of chronic kidney disease (CKD) was identified from KPMAS' CKD registry. Patients could develop the condition during the study period or have a history of CKD. We operationalized end-stage renal disease in the same way.

We collected data that indicated the presence of a substance use disorder (SUD) that was operationalized as the number of encounters for an SUD based on diagnosis codes. Number of substance abuse encounters ranged from 0 to 246. If a patient had any non-zero amount of encounters, we considered the patient to have a confirmed diagnosis of a SUD. There is significant discussion in the literature surrounding the higher likelihood of contracting, or transmitting, the chronic infection as a result of drug or alcohol abuse [1] and the influence of this condition on treatment success.

We constructed a composite measure based on the count of the comorbidities collected for this study. Specifically, we only included comorbid conditions that are most relevant to, or most likely to be experienced by, HCV-infected patients.

Our composite measure was constructed as a count of comorbid conditions ranging from zero to a total possible eight baseline comorbid conditions. We also explored alternative ways to operationalize the number of comorbidities a patient had at baseline as follows: three categories (0, 1-2 and 3+) and four categories (0, 1-2, 3-4

and 5-6). Included in this composite measure were the following conditions: congestive heart failure, myocardial infarction, depression, diabetes, hypertension, stroke, smoking, chronic kidney disease and end-stage renal disease. We also used the bivariate analyses to inform the construction of this index.

Liver Complications

The two primary liver complications we explored were decompensated cirrhosis and end-stage liver disease. We focused on whether or not patients had already experienced these complications upon entry into the study observation period on November 1, 2013. Based on dates of diagnosis or indication by a provider in the patient electronic health record, we determined if the patient had developed, or had been diagnosed with, these complications prior to the index date. These baseline complications were included in the analysis. If a patient with HCV has already progressed to such a severe stage where they are experiencing these complications, it may influence the likelihood of a patient receiving therapy in the 2nd-generation DAA era. Baseline liver complications were operationalized as a binary variable: a patient either had already developed complications at baseline or not.

We also identified if patients had ever developed these liver complications during the study period, however, we did not include these as possible confounders in the regression model given that their development may lie on the causal pathway. A patient diagnosed with chronic HCV may have a low Fibrosis score shortly after diagnosis but the infection may continue to progress without treatment. Once a patient's infection is so severe, they are at a risk of developing liver complications. It follows that since our primary independent variable is fibrosis score, we would not include a variable that lies on that hypothesized causal pathway as it may alter the magnitude or direction of effect.

Hepatitis C Regimens

At study start, Sovaldi (sofosbuvir) and Olysio (simeprevir) had recently been FDA approved. Harvoni (Ledipasvir/Sofosbuvir) was released about a year later in October of 2014. Viekira Pak, manufactured by Abbvie, was approved a short few months later. Given the short study period, from November of 2013 to May of 2016, and the time it takes for the uptake of new prescription drugs, the most common therapy regimens found in this study sample were Sovaldi and Harvoni. Other products have since been approved by the FDA including Daklinza,

Zepatier, Epclusa and Mavyret that received approval for other patients with other genotypes, treatment histories and varying stages of cirrhosis. There was a significant increase in number of treated patients beginning on November of 2014 when Harvoni was approved (Table 9).

Measures of Treatment Completion

We examined both persistence to therapy and cure. In order to best estimate persistence to therapy we used the therapy regimen duration based on genotype of HCV and the estimated number of weeks a patient was on a treatment regimen. An analyst-written algorithm based on the current genotype-specific guidelines determined the treatment duration. The treatment start and end dates indicated the duration of therapy the patient completed. Using these two values, in weeks, we determined if patients completed the recommended course of therapy, or were persistent, or completed less than the recommended course of therapy. We then looked at sustained virologic response (SVR), or cure, which demonstrates effectiveness in this real-world population. It is defined as the absence of detectable HCV RNA in the blood serum after therapy is complete and is measured at 12 weeks after therapy completion. A positive SVR indicates a patient had successfully cleared the virus.

Statistical Analysis:

All analyses were conducted in STATA (Version 12, College Station, TX). We conducted bivariate analyses to examine the distribution of the independent variables across the treated and untreated groups of patients. This included cross-tabulations, Chi-squared tests, and Fisher's exact tests to determine any significant differences across study groups. Further, we examined Kaplan-Meier curves as part of the nonparametric analysis to explore possible differences in survival curves between baseline categorical variables. These variables included gender, age category, location of physician service, race, insurance type, baseline liver complications, treatment history and comorbidities.

As part of our exploratory steps, we examined the types of providers, their age and specialties that treated patients with DAA. We described these characteristics for the providers that were responsible for writing the prescription for a direct-acting antiviral therapy. We did not include these provider characteristics in the model since we did not have prescriber characteristics for patients who were not treated. The providers who saw HCV patients

that remained untreated would not serve as an adequate control for the specialists that prescribed DAAs to the treated patients. With only 980 patients treated, we would have about 66% missing information on patients and we would not be able to predict who these patients would have seen in order to access DAA therapy.

We also examined persistence to therapy and sustained virologic response by patient demographic characteristics and comorbidities. This analysis allowed us to explore any disparities in cure rates or therapy completion rates by the presence of certain comorbidities or demographic characteristics. We also compared effectiveness in this study sample to efficacy rates from clinical trials.

The primary multivariable regression analysis we used was a semi-parametric cox proportional hazards model to conduct a survival analysis. Analysis time was treated as continuous and considered time from the index date. The overall study start date was 11/1/2013 – or the time point at which the second-generation DAAs became available. An individual patient's index date depended on whether they were a prevalent or incident case of HCV. A patient was a prevalent case if their diagnosis date was before the study start date and an incident case if their diagnosis date was anytime after the study start date. The resulting model produces hazard ratios indicating differences in the rate of being treated for patients with different characteristics. A hazard ratio can also be interpreted as an increase or decrease in the risk of the outcome of interest – treatment initiation.

We conducted a sensitivity analysis by analyzing prevalent and incident cases separately to see if there were any different influences on treatment initiation. The differences in the makeup of the pharmaceutical market may make a difference.

Results

6,000 patients are currently in care and followed in the KPMAS HCV registry. We limited our study to patients who had not successfully been treated with a previous drug regimen and had not yet been treated with a new DAA. Table 1 outlines the specific criteria we used for a confirmed HCV diagnosis. After limiting the study sample to those who met our definition for continuous enrollment prior to study start date, November 1, 2013, we had a total of 3,017 patients. After excluding patients who did not have any measure of fibrosis, Fibroscan or Fib-4 tests, after the designated baseline date, our final study cohort included 2,962 unique patients (Figure 1).

Patient Characteristics:

Overall, about 33% of the study cohort was treated with a new DAA over the course of the study period. Figure 2a shows the non-parametric Kaplan-Meier survival curve for the entire study sample. Survival indicates that a patient has *not* received treatment by a certain point in the study period. About 66% of the study sample has *survived* by the end of the analysis time – indicating about one-third initiated treatment.

Table 2 describes the study population by treatment status – patients are "treated" if they were treated at any time over the course of the study period and "untreated" if there was no indication of a regimen start date from the prescription records. The distribution of gender, patient's state of residence and race were similar across treatment groups. Treated patients were slightly older than untreated patients and therefore makes sense that there were likely more patients covered by Medicare in the treated group. A higher percentage of treated patients were treatment naïve, or had never been treated with any drug regimen, than those in the untreated group. Further, there were more incident cases that were treated during our study period than in the untreated group. About one-third of each of the treatment groups had zero comorbidities of interest at baseline. Slightly more patients in the untreated group had greater than 4 comorbidities. Majority of the patients in our cohort had not developed any liver complications by the time of study start, however, patients in the untreated group had a slightly higher number of patients that had developed at least one by the time they entered the study. There was a significant difference in the provider service area across treatment groups, with more of the treated patients in the District of Columbia and Southern Maryland area and more of the untreated patients in the Baltimore area. Given that we could only access the medication claims on patients within the KPMAS system, we did not capture any referrals to any prescribing physicians outside of this health care network. Based on communication with C. V. Rodriguez, from unpublished data showed that 31% of RNA positive patients not linked to care within the KPMAS system had a referral to a non-KP specialist and 78% of these were Baltimore patients.

There were 51 patients in our sample that were co-infected with Hepatitis B virus, however the distribution of HBV co-infection across treatment groups was not statistically significant ($p=0.793$). Majority of the sample (88%) had genotype 1. Further, majority of the treated patients were GT 1 (90%). This was expected as the treatments available during our study period, Sovaldi and Harvoni, were approved for patients with GT 1 HCV. We did find some significant differences in treatment by genotype (Table 2).

A total of 172 patients were HIV positive at baseline, however the distribution of HIV co-infection across the two treatment groups was not significant (p=0.998).

Most important to note is that 2248, of the original 2962, patients had what we defined to be a baseline F-score. We found 2079 patients that had two or more F-scores during the study period and a total of 128 patients had no F-scores at any point.

Of the patients with F-scores derived from the transient elastography (TE), 36 had two or more scores. This small number of patients with multiple scores from a TE is not unexpected, as the Fibroscan became part of routine HCV care in early March 2015 – about halfway through the study period. Patients underwent a TE much more infrequently than Fib-4 assessments – the mean time difference between the TE scores was about 259 days with a median time interval closer to a year at 343 days.

Overall, the mean change in scores for patients with more than 1 F-scores during the study period was 0.871 and had a median of 1. The variance around these differences is .956. While we hypothesized that the F-score metric would be a substantial driver of treatment, the distributions across treatment groups are similar (Figure 3). It is also important to remember that follow-up period for patients varied – while prevalent cases had a little over two years of analysis time, many incident cases had as short as six months of time on the study (Figure 4). In order to see changes in liver fibrosis meaningful enough to significantly influence the treatment decision, it may take years.

Comorbidities:

We quantified comorbid conditions by treatment group (Table 3). We found differences in treatment status by SUD, myocardial infarction (MI) and smoking status. We further explored the significance of these comorbidities in the multivariable analysis.

Bivariate Analysis:

Our bivariate analysis for this survival analysis included Kaplan-Meier curves to test, individually, if any of the categorical variables at baseline influenced the probability of treatment initiation. Figures 2a-2m show the survival curves for some of the baseline variables and the results of the associated log-rank tests that provide evidence of any significant differences in survival. Further, any crossover seen in the survival curves indicates no

significant difference in the probability of treatment. The log-rank test is limited in that it can provide evidence of a difference but cannot identify between which categories that difference exists.

Figure 2 shows that treatment naïve patients are more likely to be treated and the log-rank test shows that this difference is significant. Service area shows a borderline significant difference in likelihood of treatment. At baseline, we see a significant difference in likelihood of treatment across number of comorbidities when the variable is a simple count. The stepped survival curves indicate small sample sizes in some of these categories (Table 2) and so we examined Kaplan-Meier curves for the other version of the categorical variable. We also explored Kaplan-Meier curves for MI and smoking (Figure 2) given the results of the bivariate chi-squared tests (Table 3). Figure 2 shows no significant differences in probability of treatment by insurance type, gender or baseline liver complications. Race does not significantly influence the probability of treatment (Figure 2) and this remains insignificant in the multivariable analysis (Table 7).

Provider Characteristics:

We wanted to explore any association between the characteristics of the *prescribers* of the DAAs and treatment. Within KPMAS, certain specialists, such as gastroenterologists (GI) or infectious disease (ID) physicians, are the primary prescribers of DAAs – when patients meet certain clinical criteria, they are immediately triaged to see a GI or ID specialist who, along with the patient, makes a treatment decision. This cascade of care was implemented at KPMAS in 2015. We would not observe a prescribing physician for the untreated patients in our study. These patients may never have had the opportunity to see a physician that would prescribe a DAA. We did not want to use the primary care physician the untreated patient last saw during the study since a patient could have seen multiple primary care physicians within the KPMAS network. This missing data issue, where the prescriber variables are missing *not at random*, would show systematic differences in providers for treated and untreated patients.

Our exploratory analysis of prescriber characteristics indicated some deviation from the care pathway indicated above. This could also be why the distribution of F-scores across the two treatment groups is similar – a specialist is not necessarily just treating patients when they exceed a clinical threshold. About 47% (34) of the physicians specialized in internal medicine gastroenterology, 14% (10) specialized in infectious disease and 7% (5)

were adult primary care internists (Table 4). Other specialties included pediatrics, family practice, urgent care, ophthalmology, adult neurology, internal medicine hospitalist, emergency medicine, psychiatry, obstetrics/gynecology, anesthesiology and internal medicine endocrinology. There were a total of 71 unique prescribing physicians that treated the 980 patients that were treated in our study cohort. The majority of these physicians had an MD (n=69), while only two of these physicians were doctors of osteopathic medicine. Majority of the physicians were between the ages of 31-50 (~70%) with one physician under 30 and seven above 60. If patients with chronic HCV have other complications or multiple comorbidities, providers other than liver specialists may play a role in ensuring greater access to DAAs.

Persistence:

Of a total of 980 patients treated during the study period, 958 (97%) patients were persistent to their DAA regimen (Table 5). We found no significant differences in persistence by gender, state of patient residence, race and case type. However, we found that there was a significant difference in persistence to therapy by age and baseline F-score. Further, we found some significant differences in rates of persistence by presence of hypertension and end-stage liver disease. Specifically, treated patients with hypertension experienced a higher percentage of persistence to DAA therapy while treated patients who had already developed end-stage liver disease by study start had a lower percentage of patients that were persistent to therapy. It could be that patients with hypertension are monitored closely for other therapies they have been prescribed and therefore have more contact with a physician who can closely monitor their treatment course. Patients who have already developed end-stage liver disease may have increased difficulty completing their medication regimen. While majority of the treated patients were genotype 1, 15 of these patients completed less than the recommended course of therapy. All patients with genotype 2 and 4 completed therapy. While all the HBV co-infected patients who were treated were persistent to therapy, only one of the 57 patients co-infected with HIV at baseline was not persistent to therapy.

It is important to note that 22 patients were not persistent in this study cohort. Six of these patients have a regimen stop date beyond the end of the study date and so this is attributable to the time periods during which data was collected and used for this particular observational period. This leaves 16 patients that did not meet our definition of therapy persistence, or completion. Although there was no statistically significant difference in rates of

persistence by these conditions (Table 5), nine of these patients had a baseline diagnosis of SUD and six were smokers – they could have had some clinically meaningful influence on persistence to therapy. Although a small percentage of the total number of patients treated, this is a substantial amount of cost to the system.

Sustained Virologic Response:

There were 776 patients that had an indicator of sustained virologic response (SVR) of which 738 (95%) patients successfully achieved cure. This result demonstrates real-world effectiveness of these therapies - clinical trials for new therapies found cure rates of about 95% or higher. [126, 127] We found no significant differences in achievement of cure by gender, age, race, state of residence, case type, genotype or HIV co-infection (Table 6). We found some differences in percentage SVR between patients who did and did not have a specific comorbidity, but none were significant. Furthermore, none of the patients who had CKD or ESLD at baseline were treated and so we could not explore any possible differences here. These results are important given that the current AASLD treatment guidelines recommend treating everyone – similar rates of cure across subgroups of our study sample support these guidelines for physicians.

Multivariable Analysis:

The semi-parametric cox hazards model provides hazard ratios that indicate differences in the "risk" of treatment with a DAA. A hazard ratio above 1 indicates an increased risk of treatment and below 1 indicates a reduction in the risk of treatment. We see that the primary variable of interest, F-score, at baseline, shows no significant association with the hazard of treatment initiation (Table 7a). Further, the time-varying F-score also shows no significant influence on the decision to treat. Given the descriptive statistics around the change in F-scores over time and baseline F-score distribution (Figure 3), it is not surprising that there was no significant influence on treatment. The maximum follow-up time for this analysis was about two years – HCV takes years, potentially decades, to develop to the most severe stages of liver disease. Further, the variability in the number of F-scores each patient had over the observational period and the change in diagnostic procedure protocol at KPMAS may also have limited the consistency with which fibrosis was measured over time. The changes in F-score may not have been significant enough to influence physician treatment choice.

We do find, however, that age is a significant predictor of treatment initiation. Patients aged between 40-60 years and 60-80 years both experienced increased likelihood of treatment in comparison to the youngest patients. Older patients may be sicker, or their fibrosis may be more advanced, which could drive treatment. Neither race nor gender had a significant association with treatment indicating more equitable access to care in this setting. State of residence did not influence the probability of treatment, however, service area was a significant predictor of treatment. The service area variable provided a more accurate depiction of practice environment since KPMAS has care settings across three states and there could be some variability even within the larger health system. Some previous studies in KPMAS found that many HCV patients in the Baltimore area received referrals for their specialist care to non-Kaiser Permanente physicians. Given that we did not capture any medication claims outside of KPMAS, it may appear that patients in the other two primary service areas are more likely to receive treatment.

We found no significant differences by insurance status - additional evidence that supports equitable access to care. The differences we observed in the bivariate analyses by treatment history disappear in this multivariable analysis after controlling for other covariates. When we construct the baseline liver complications variable as a binary indicator, we don't see any differences in probability of treatment by the presence of any of these conditions, which is consistent with the bivariate analyses.

In this model, with the baseline comorbidity index constructed as a simple count, we did not find any significant differences in the hazard of treatment. We found that a confirmed diagnosis of SUD did lead to a significant decrease in the risk of treatment. This is also consistent with the unadjusted bivariate analyses and the effect remains substantial after controlling for other covariates. While the AASLD recommends treating these patients and the literature shows this population can be just as adherent [128-130], there may be the fear of potential re-infection. This is of particular policy interest as some payers would like to see any kind of SUD controlled prior to covering these new therapies – re-infection would mean requiring re-treatment which increases costs.

We did not find any differences in hazard of treatment by HBV or HIV status in the adjusted model. We did, however, find that patients with genotypes 2 (HR:0.699, 95% CI: 0.495,0.987) or 3 (HR:0.607, 95% CI: 0.382,0.967) were less likely to be treated than those with genotype 1. No patients with genotype 5 were treated.

We also found that case type – prevalent or incident – was a significant predictor of treatment. Incident cases had an increased likelihood of being treated with a new DAA. While this association does not remain

significant in the multivariable analysis, it is reasonable that patients being diagnosed after the new DAAs became the standard of care are more likely to be treated given the new treatment choice set.

Sensitivity Analyses:

After finding case type to be significant in the original analysis, we analyzed these two sub-samples of our cohort separately (Table 7c-d). In the prevalent cases, we found the same associations to be significant with treatment initiation. In the incident cases, we see that the significant association of treatment with service area and age we saw before disappeared. It is possible that cases diagnosed earlier may have been referred out to clinical trials. In the exploratory analyses, we did find that patients were younger in the incident cases subgroup and so this may have impacted the association of treatment with age. Further, baseline HIV co-infected was significantly associated with an increased likelihood of treatment in the incident cases (p=.037). The association between genotype and treatment disappear in both of these subsample analyses. We still see a significant association of the hazard of treatment with having one or two comorbidities and having a SUD. Both of these reduced the hazard of treatment.

We reconstructed the simple comorbidity count to a categorical variable in which a patient could have zero, 1-2 or three or more comorbidities at baseline and found this largest category to significantly increase a patient's hazard of treatment (Table 7b).

The primary hazards model included both baseline smoking and myocardial infarction as part of the baseline comorbidity categorical variable. However, unadjusted bivariate tests showed that there was a difference in treatment status by patients who were smokers at baseline and those who had suffered a myocardial infarction prior to study start. We conducted a sensitivity analysis by constructing a hazards model to explore the individual association between each of these comorbid conditions and the hazard of treatment by removing them from the comorbidity index (Table 7e). The associations found with age, service area, SUD and genotype remain, while the association with the comorbidity index is no longer significant. However, we do see that having had a myocardial infarction at baseline, prior to the beginning of the study period, significantly reduced the likelihood of treatment. Model fit, using AIC, demonstrated that this was a better fit than grouping these two comorbidities with the rest of the conditions (Table 8). Smoking was no longer a significant predictor treatment in the adjusted model.

Strengths & Limitations:

The primary strength of this study was the longitudinal structure of the data available on patients from the electronic health records from this integrated health care system. The HCV registry at KPMAS facilitated data capture on the same patients over time and made our survival analysis of an outcome with a time component possible. Further, we were able to capture data on the primary clinical metric of interest over time – the F-score – to assess whether changes in disease severity played a significant role in the treatment decision for HCV patients in the new DAA era. We also had dates on each of the events possible for a patient – treatment, death, leaving the health plan – which enabled us to accurately capture when patients experienced our outcome of interest or if they were censored for any reason. The integrated health system allowed us to easily link and pull prescription records for patients in our sample to determine study start.

Our survival analysis method was the appropriate approach given that patients in our study sample could have initiated DAA therapy at any time during the observational period. The extensive information on the fibrosis diagnostic procedures, including test dates, allowed us to systematically identify a baseline F-score for each patient.

Given the recent developments in the pharmaceutical market for the treatment of chronic HCV, it was imperative that we examined patients exposed to this growing market to understand the predictive factors of treatment. We were able to pull the most recent data on registry patients through May of 2016.

While there were strengths to this analytic approach, there were some limitations that should be considered when interpreting our results. It is possible that SUD was underreported. The stigma around SUD and the high prevalence of HCV amongst injection drug users may have introduced some bias into our analysis by underestimating the number of individuals who have a SUD. Specifically, our estimates of the association between SUD and initiation of treatment may be conservative. There may be an even greater difference in likelihood of treatment based on the type of SUD a patient has (drugs or alcohol) which each have their own implications for liver disease and the transmission of HCV infection. The extent of the disorder, or how long the patient has had an SUD, may also influence into the treatment decision given that physicians may consider their patients' ability to remain compliant to therapy.

There was also likely some missingness around the treatment history variable. Patients could have been treated prior to the study start date but this prior treatment may be missing if they joined the Kaiser Permanente

Health Plan with an existing HCV diagnosis. Specifically, we created treatment indicators from treatment regimen start and end dates and if those were not appropriately recorded in the electronic health record, we may have missed this. Further, we pulled DAA treatment information from regimen start and stop dates and calculated persistence according to an algorithm based on treatment guidelines from the KP Inter-Regional Hepatitis Working Group and the AASLD. Patients may have actually been on therapy more or less time than recorded, which would have changed the category of persistence to which the patient was assigned. For example, if a genotype-specific regimen indicated a patient should be on 12 weeks of therapy, but in reality, the physician only indicated 8 weeks of therapy to the patient, our data would assign this patient to the "non-persistent" group if they only completed 8 weeks.

A significant limitation was the lack of a baseline F-score for a substantial amount of patients. We had to derive F-scores from two types of diagnostic procedures. While the results from the transient elastography can be mapped onto F-scores, the results from the Fib-4 are less clearly translated. Further, the incorporation of the transient elastography into protocol at KPMAS became official in March of 2015 and so there was some change in how chronic HCV was assessed during the course of our observational period. This variation could have influenced the consistency with which F-scores were recorded over time and the variability in the amount of F-scores available for each patient. The limited amount of follow-up time for about half of the patients in our study sample (Figure 4) also prevented us from fully capturing any significant changes in fibrosis over time.

Policy Implications & Discussion:

This study is incredibly timely given the recent attention around high drug prices – the costly new HCV treatments epitomize the political and policy discussions around reducing spending on prescription drugs in this country. Gilead's blockbuster drug, Sovaldi, was initially priced at $84,000 per regimen. Given the high rates of infection amongst low-income individuals, patients without adequate health insurance coverage are vulnerable to significant financial burden to treat their now curable condition.

Restrictive state Medicaid access policies spurred the controversy over "rationing care" in the United States given the AASLD [1] has recommended that all patients diagnosed with chronic HCV be treated with the new DAA therapies. The significant improvement in effectiveness of these new drugs over the old standard of care makes them a profound clinical and public health victory. In response to pushback by patients, providers and lawmakers, many

state programs have eased their coverage criteria. [131, 132] Many states have eased their liver disease, sobriety and prescriber requirements between 2014 and 2016. While variability of these restrictions still exists that lead to varying levels of access to care, one key improvement over time has been the transparency in these restrictions that can help in evaluating the effects of these restrictions. [1] The triaging of patients due to financial barriers is more controversial given that the providers and payers do not place patients with other severe diagnoses, such as cancer, in the same difficult situation of waiting for treatment coverage.

Health systems may also vary in how they treat their patients. KPMAS, for example, has published its care pathway for HCV patients. [133] The incorporation of an HCV care coordinator of HCV patients ensures continuity of care for this slowly progressing chronic disease. KPMAS does not restrict DAA treatment to patients in the same way that others might, but they do structure their care pathway so that patients with the most severe liver disease are referred to specialists for immediate assessment while primary care physicians monitor those with lower fibrosis scores over time. However, in our study, we did not find a significant difference in the distribution of F-scores across the treated and untreated groups suggesting that the KPMAS system might be doing better on this metric of access than others. KPMAS is unique in its integrated setting allowing for greater continuity of care over time and evident by its various patients registries allowing providers the opportunity for longitudinal follow-up. Although it might not be representative of patient experiences in other care settings or health plan environments, it provides a picture of what can be a model of efficient HCV care.

Providers and policymakers can view these results as an opportunity to better understand why patients with substance use disorder, patients with a history of heart disease or smokers may be less likely to be treated in spite of universal treatment guidelines from the AASLD. The national guidelines indicate that the DAA therapies are the new standard of care and that all diagnosed patients should be treated. There are both ethical and economic arguments for universal coverage but the most compelling argument is presented by leading public health advocate Congressman Henry Waxman, in a letter [134] to the Chief Executive Officer of Gilead Sciences Inc., where he highlights a widespread concern that “a treatment will not cure patients if they cannot afford it.” Further, it’s not just Gilead’s product Sovaldi that was priced so highly – each of the subsequently manufactured and approved DAAs were priced in the same magnitude minimizing affordability for patients with even the most generous drug plans.

Even Mavyret, the latest pan-genotypic therapy approved in late 2017, has a list price of $26,5000 – comparatively cheaper, but still high enough to warrant a continued pharmaceutical policy discussion.

Even more compelling are the consequences to delaying therapy without adequate or appropriate monitoring of a patient's hepatic function or enzyme levels. While integrated systems like KPMAS have care navigators and longitudinal data mechanisms to follow patients closely, other providers or hospitals may not be able to monitor their patients over time. Missing the ideal window for treatment may cause more severe long-term liver sequelae to develop – the clinically and economically burdensome manifestations of the infection. Treating chronic HCV has the potential to generate long-term savings, although more studies with longer follow-up than this study will be required to demonstrate that.

Our study found that patients with a history of a SUD were less likely to be treated. Although there may be hesitancy on part of providers to treat injection drug users given their possibility of relapse or reinfection with the continued use of injection drugs, there is literature that counters these common arguments. Studies have shown that even with interferon-based therapies, there isn't much of a difference in adherence to therapy between those who inject and do not inject drugs. [128-130] The medical community recommends, ideally, that treatment for HCV-infected persons who inject drugs should be provided in a multidisciplinary setting with services not only for the treatment of HCV, but to help manage common social and psychiatric comorbidities in this particularly vulnerable population. [1] Further, an understanding of the disease itself and treatment options available amongst patients in this population is also necessary to connect vulnerable patients to appropriate care. [135] KPMAS is uniquely positioned to provide this kind of care – however, the potential for underreporting of SUD given the stigma [136-138] around the disease or the difficulty in diagnosing the condition may prevent the resources from fully being utilized. Some modeling studies [139] have demonstrated a high return on investment of treating this particularly susceptible population. Appropriately screening, diagnosing and linking to care individuals who inject drugs can make a major impact on the HCV epidemic in the United States.

Although our study found differences in likelihood of treatment, we did not find any significant differences in persistence to therapy or achievement of SVR– likely due to minimal side effects and higher rates of efficacy of the new agents. [126] However, we looked at overall or any substance use disorder, but further work could focus on either alcohol or drug abuse and better understand the nuances of these different types of disorders and their

relationship to the success of HCV treatment. Many health plans have in place sobriety requirements for their beneficiaries and future work could help to inform more appropriate or evidence-based access to DAA treatment.

Patients with a history of a myocardial infarction had differences in probability of treatment. Research has shown the association between HCV and an increased risk of different types of cardiovascular disease (CVD) citing the infection as an independent risk factor. There is some literature around the possible influence of interferon-based treatment for HCV on the risk of vascular disease. [140, 141] Interferon-based therapies, however, are no longer the standard of care and have been replaced by the second-generation DAAs. It is still too soon to understand the long-term implications or risks on chronic HCV patients regarding any cardiovascular events. A recent study by McKibbon et al. assessed the association between chronic HCV and cardiovascular disease – specifically looking at subclinical coronary atherosclerosis. Using the Multicenter AIDS Cohort, they evaluated associations of chronic HCV and HIV infection with "metrics of plaque prevalence, extent and stenosis." Even after adjusting for HIV status, and other patient characteristics, researchers found a significant association between chronic HCV infection and increased prevalence of heart disease and presence of plaque buildup in arteries. [142] Many of the men had an HIV infection and HIV/HCV co-infection has been shown to be associated with an increased risk of CVD. [143] However, the researchers found an independent association with CVD similar to the findings in other studies. [144, 145] This further supports the need to treat chronically infected patients earlier in the progression of disease and the need for future, longer-term follow-up studies to determine the effect of DAA therapy on risk of heart disease. [145]

In the context of our study, we need to better understand why those patients with a history of a myocardial infarction had a decreased likelihood of treatment. However, we found no differences in persistence to therapy or achievement of sustained virologic response. Only a few patients, comparatively to the overall sample size, had a history of an MI (21) and may be contributing to the significant finding.

Our initial bivariate analysis found that patients with a history of smoking experienced a decreased likelihood of being treated with a DAA. However, the adjusted analysis did not find this factor to be a significant predictor of treatment. These mixed findings reflect the literature on this association. Some studies suggest that chronically infected HCV patients who smoke have been shown to have significantly higher chances of developing hepatocellular carcinoma (HCC). [146-148] A meta-analysis by a group of researchers found interactions between HCV infection and cigarette smoking that may influence the risk of HCC. [149] Amongst studies examining the interaction

between HCV infection and smoking, they found that the relative risk of HCC was 23.1 (95% CI: 9.43 – 56.8) for patients who smoked and had chronic HCV – this is a fifteen-fold increase over the risk of developing HCC for smokers among HCV negative patients. [149] However, other literature focusing on HIV/HCV co-infected patients indicate that smoking has no impact on liver progression over time. [150] Liver cancer is one of the most clinically and burdensome long-term sequelae that can develop from a chronic HCV infection [44] – the development of which the new DAAs have been hypothesized to prevent.

Again, we found no difference in persistence to therapy or achievement of SVR by smoking status. Some previous studies in the interferon-era [151] have shown adherence did not differ by smoking status, while others have found that smoking has a negative impact on antiviral therapy in naïve patients with genotype 1. [152] Specifically, smoking significantly reduced the response rate to therapy, but the new DAAs may change this. [152] Studies with longer follow-up and more nuanced information on smoking status will be necessary to provide real-world effects of the DAAs in this particular population.

According to the Census Bureau, the proportion of the United States population comprised of minority populations is projected to rise from 38% in 2014 to 56% of the total population in 2060. With the growing diversity of the American population, providing equitable access to care is increasingly important. As chronic HCV is prevalent among the most vulnerable populations, not just by race or ethnicity, the health care system should work to ensure these patients have access to the treatments they need. While some previous literature highlights some disparities in treatment and development of chronic HCV by race, this study provides evidence the opposite is occurring at KPMAS – we did not find any differences in probability of treatment with DAAs across race after adjusting for other others. Further, Rodriguez et al. also explored time to treatment through the year 2014 at KPMAS and found that race was not a significant predictor of interferon-based or DAA-based therapy. [153] However, a recent study by Kanwal et al. using the Veterans Administrations national database found differences in the receipt of new DAA therapies by race and gender. Specifically, the authors found that Black patients had lower odds of receiving DAA treatment than White patients and women were also less likely to receive treatment than men. [75] Others have found, in other health care settings, that differences in exposure to HCV and screening exist by race [154] – while providers and systems may not have control over a patient's exposure to the virus, we do have the ability to ensure that regardless of demographic characteristics, a diagnosed patient has access to appropriate and timely care.

GT 1 was associated with an increased likelihood of therapy, compared to patients with GT 2 or 3. This was expected since majority of the study sample had a GT 1 infection and the DAAs approved during this study period were indicated for GT 1. HIV status was only a significant predictor amongst incident cases. Rodriguez et al. found similar results when looking at a patient sample through the year 2014 at KPMAS. [153]

Conclusion

While this work focuses on a specific and unique patient population, there is a great deal of work that remains to understand the nuances of treating patients with chronic HCV in the new DAA era. The limited side effects, ease of administration and curative nature of these therapies has made them the new standard of care. From a public health perspective, treating as many patients with this infectious disease can reduce the incidence of this chronic condition with the ultimate goal of HCV eradication in mind. It is critical to understand the treatment patterns of this patient population given they are susceptible to various advanced liver sequelae. Future work can contribute to this growing literature focused on predictors of treatment in different patient populations to understand the underlying determinants of the differences in therapy choices.

While the financial burden continues to be discussed as a possible barrier to care, future work should aim to assess the impact of DAAs on economic outcomes to provide estimates of potential savings, or spillover benefits, from DAA therapy. The following analysis explores the impact of treatment on healthcare resource utilization during the post-treatment follow-up period.

Tables & Figures

Figure 1: Patient Inclusion Flow Chart

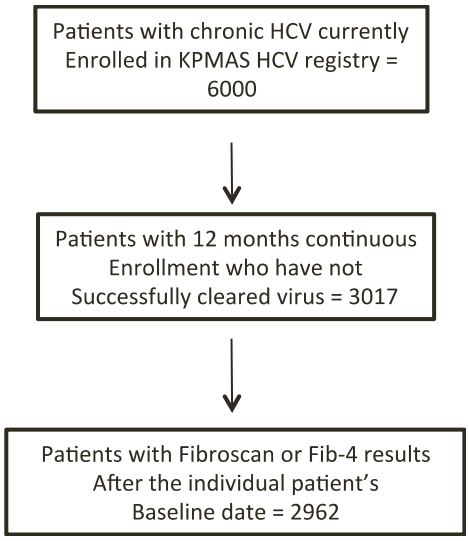
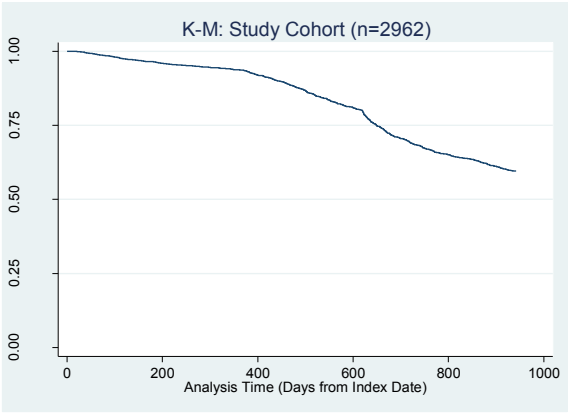
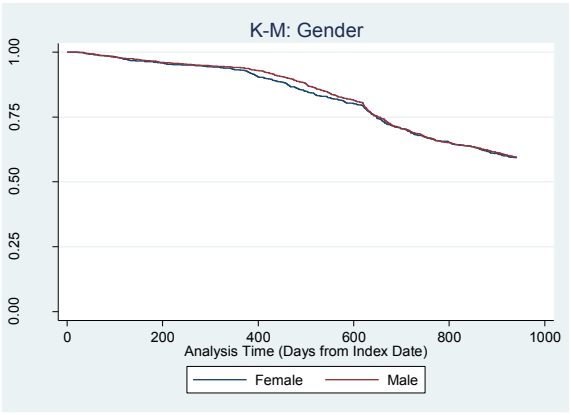


Table 1: Clinical Patient Inclusion Criteria

Criterion 1: Positive HCV RNA results (either as "positive" if HCV RNA qualitative or level above lower limit of quantification if HCV RNA quantitative)
Criterion 1a: HCV genotype with published result NOT negative (which implies quantifiable HCV RNA in sample
Criterion 2: Two or more prescription refills of anti-HCV drugs within 365 days (It could be a patient who had two (2) or more prescriptions of the same anti-HCV drug dispensed within 365 days of each other, or one (1) prescription of two different anti-HCV drugs dispensed within 365 days of each other. Ribavirin will count if it has two or more prescriptions dispensed within 365 days but one prescription of ribavirin and one of another would not be okay because it acts as a booster for the other anti-HCV drug that is prescribed along with it.
Criterion 3: Positive Hepatitis C antibody and 2 or more HCV negative RNS tests after the first positive Hepatitis C antibody test.
Criterion 4a: A patient with a positive HCV antibody test PLUS 2 or more outpatient HCV coded visits by GI (Gastroenterology, GAS) or ID (Infectious Diseases) providers (Using earliest result date of AB lab test account for the patient)
Criterion 4b: Positive HCV antibody test PLUS 2 or more outpatient HCV coded visits by provider NOT GI or ID (Should be two or more visits to non-GI or non-ID provider, this also counts only one GI/ID and one or more non-GI/ID provider. Using earliest result date of AB lab test account for the patient).
Criterion 5: Positive HCV antibody test PLUS only 1 outpatient HCV coded visit by any provider (Using earliest result date of AB lab test account for the patient).

Figure 2a-m: Bivariate Analyses – Kaplan-Meier Curves





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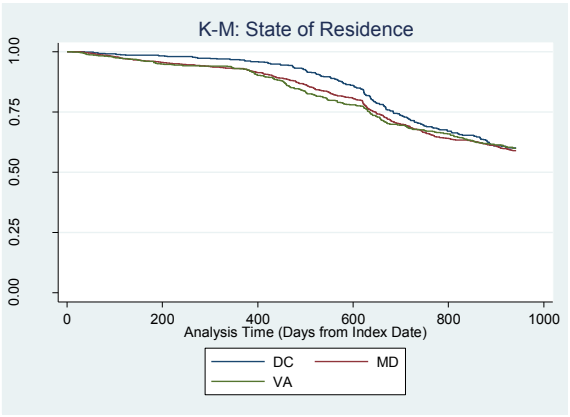
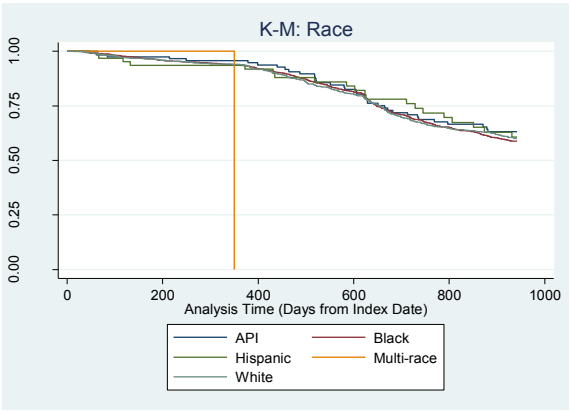
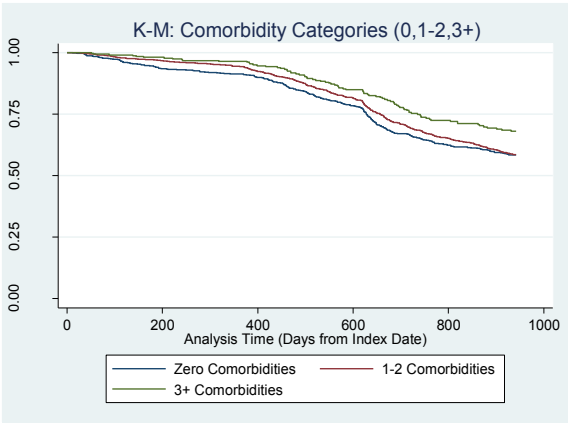


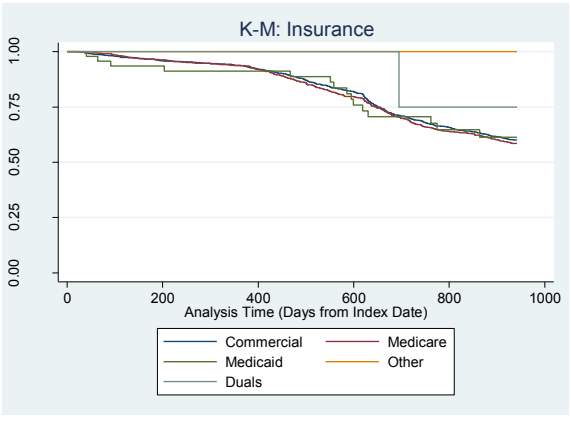
p=.5047



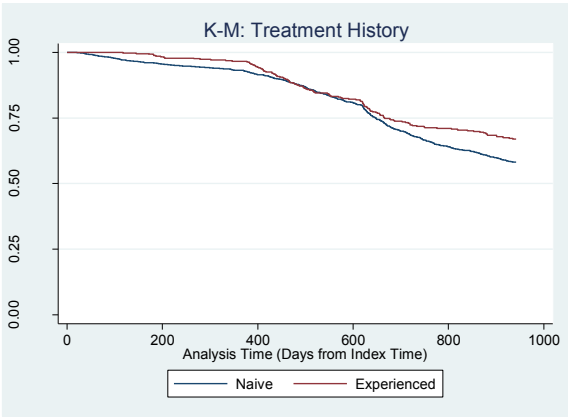
p=.0067



p=.0086



p=.7026



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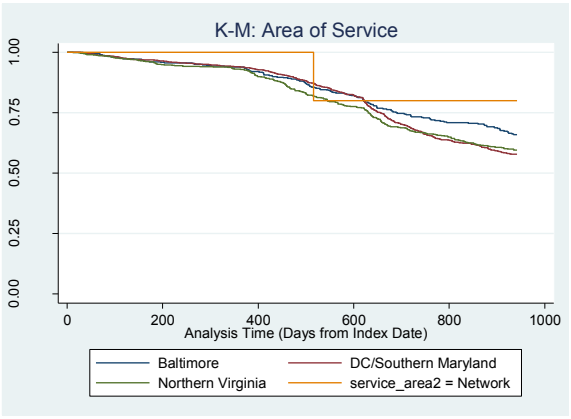

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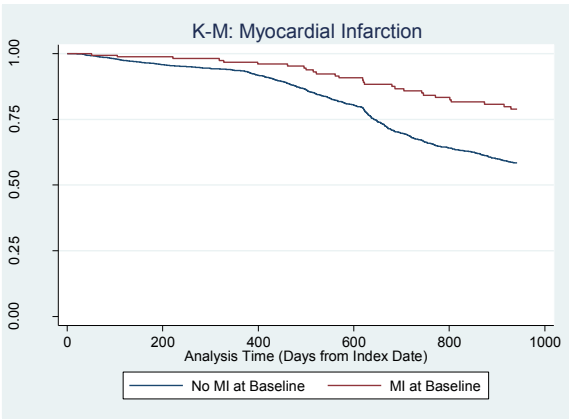
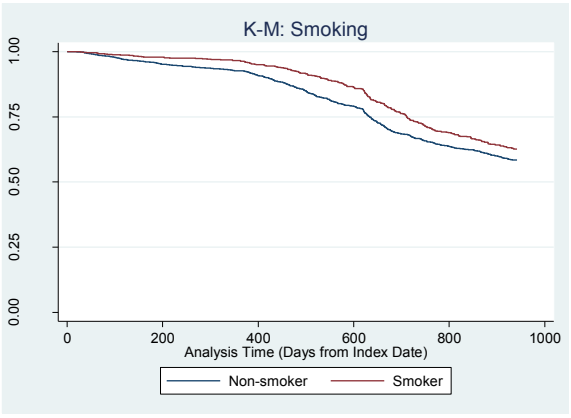
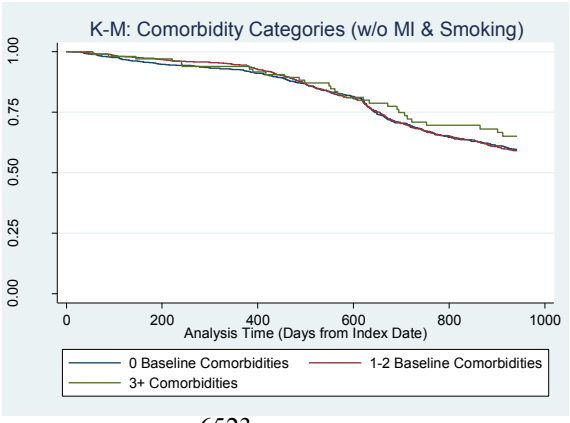


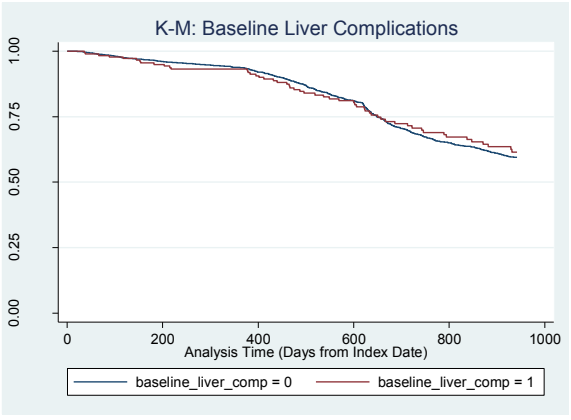
p=0.000



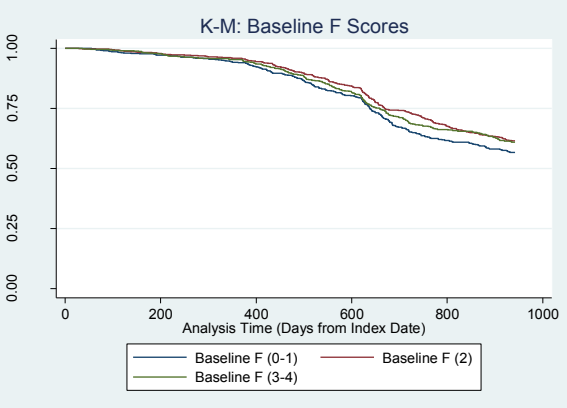
p=.0051



p=.6523



p=.8105


K-M: Baseline F Scores
1.00
0.75
0.50
0.25
0.00
0
200
400
600
800
1000
Analysis Time (Days from Index Date)
Baseline F (0-1)
Baseline F (2)
Baseline F (3-4)

p=0.0971

Table 2: Study Cohort Baseline Characteristics (n=2962)

Covariates	Treated	Untreated	P-Values
Gender			
Male	611 (62%)	1253 (63%)	
Female	369 (38%)	729 (37%)	**p=.644**
Age Category			
20-40	17 (1.7%)	85 (4.2%)	
41-60	414 (42%)	858 (43%)	
61-80	545 (55%)	990 (50%)	
81-100	4 (.4%)	48 (2.4%)	**p=0.00**
Patient State of Residence			
DC	180 (18.4%)	380 (19%)	
MD	560 (57.2%)	1107 (56%)	
VA	238 (24%)	479 (24%)	**p=.820**
Race			
API	36 (3.8%)	83 (4.4%)	
Black	579 (61%)	1159 (61%)	
Hispanic	20 (2.1%)	45 (2.3%)	
Multi	1 (.1%)	0 (0%)	
White	311 (33%)	618 (32%)	**p=.610**
Insurance Type			
Commercial	604 (62%)	1263 (64%)	
Medicare	360 (37%)	666 (34%)	
Medicaid	15 (1.5%)	31 (1.5%)	
Other	0 (0%)	19 (.9%)	
Duals	1 (.1%)	3 (.1%)	**p=0.019**
Service Area			
BALT	137 (14%)	373 (18%)	
DCSM	598 (61%)	1124 (56%)	
NOVA	244 (25%)	479 (24%)	
Network	1 (.1%)	1 (.05%)	**p=0.006**
Baseline F			
1	247 (33%)	430 (28%)	
2	299 (40%)	634 (42%)	
3	208 (27%)	430 (28%)	**p=.148**
Comorbidity Category (version 2)			
0	294 (30%)	542 (27%)	
1 or 2	603 (61%)	1191 (60%)	
3+	83 (8.5%)	249 (12.5%)	**p=0.003**

Covariates	Treated	Untreated	P-Values
HCV Tx History			
Naïve	855 (87%)	1668 (84%)	
Experienced	125 (13%)	314 (16%)	**p=.026**
Case Type			
Prevalent	821 (84%)	1721 (87%)	
Incident	159 (16%)	261 (13%)	**p=.025**
Genotype			
1	881 (90%)	1351 (86%)	
2	44 (4.5%)	108 (6.8%)	
3	23 (2.3%)	66 (4.2%)	
4	16 (1.6%)	22 (1.4%)	
5	0 (0%)	2 (0.1%)	
6	7 (0.7%)	19 (1.2%)	**p=0.008**
Comorbidity Count			
0	294 (30%)	542 (27%)	
1	376 (38%)	719 (36%)	
2	227 (23%)	472 (24%)	
3	70 (7%)	195 (9.8%)	
4	12 (1%)	49 (2.5%)	
5	1 (.1%)	4 (.2%)	
6	0 (0%)	1 (.05%)	**p=.033**
Baseline Liver Complications			
0	927 (94.5%)	1848 (93%)	
1+	53 (5%)	134 (7%)	**p=0.154**
Baseline Liver Categories			
DCC	5 (9%)	34 (25%)	
ESLD	3 (5.6%)	8 (6%)	
Liver Cancer	16 (30%)	73 (54%)	
Liver Tx	29 (54%)	19 (14%)	**-**
Baseline HBV Co-infection			
HBV co-infection	16 (1.6%)	35 (1.7%)	
No HBV Co-infection	964 (98.4%)	1947 (98.3%)	**p=0.793**
Baseline HIV			
HIV Positive	57 (5.8%)	115 (5.8%)	
Not HIV Positive	923 (94%)	1867 (94.2%)	**P=0.998**

Figure 3: Distribution of F-Scores at Baseline by Treatment Status (0=Not Treated, 1=Treated)

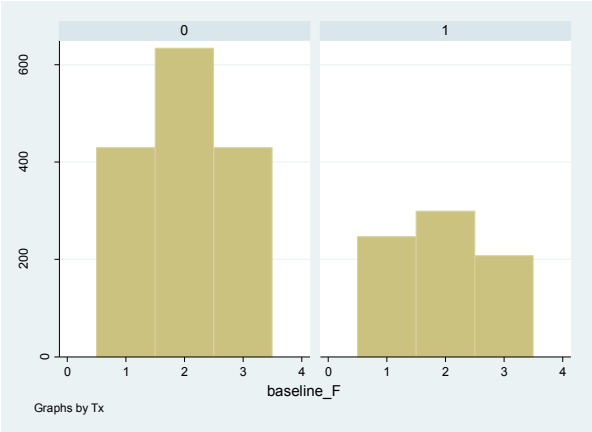
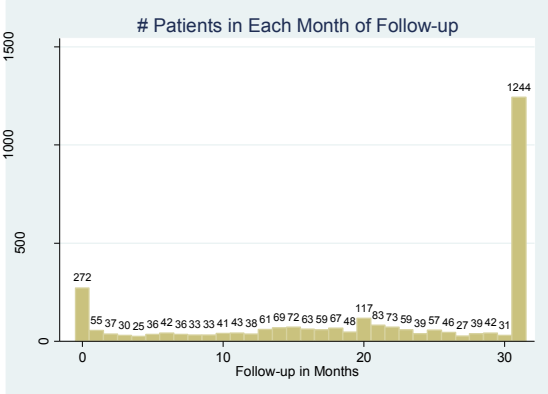


Figure 4: Distribution of Follow-up time



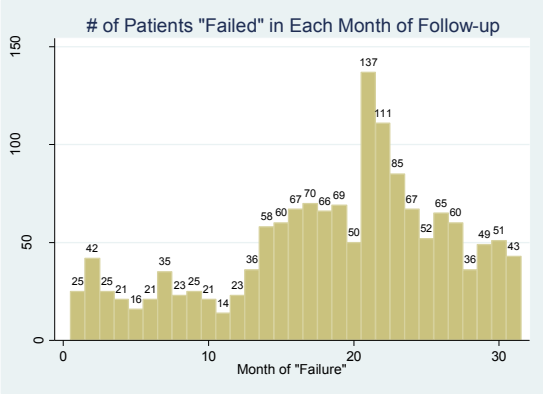


Table 3: Comorbidities by Treatment Status (n=2962)

Distribution of Comorbidities at Baseline			
Baseline Comorbidities	**Treated**	**Untreated**	**Chi^2**
Stroke (n=88)	25	63	0.344
Depression (n=280)	89	191	0.627
Hypertension (n=1458)	479	979	0.791
MI (n=169)	27	142	<0.01
Diabetes (n=719)	235	484	0.793
CHF (n=13)	2	11	0.174
Smoking (n=834)	236	598	0.001
CKD (n=1)	0	1	0.482
ESRD (n=1)	0	1	0.482
Substance Abuse Encounter (n=983)	266	717	<0.01
Liver Cancer (n=116)	34	82	0.378
Liver Tx (n=48)	29	19	<0.01
ESLD (n=18)	7	11	0.6
DCC (n=46)	6	40	0.004
Baseline Liver Complications (Liver Cancer, Liver Tx, ESLD, DCC)	53	134	0.154

Table 4: Provider Characteristics of Treated Patients (n=72)

Degree Type	**Freq**	**Percent**
MD	69	95.83
DO	2	2.78
NP	1	1.39
Specialty	**Freq**	**Percent**
Int Med Gastro	34	47.89
Int Med Adult Primary Care	5	7.04
Pediatrics	2	2.82
Family Practice (w/o OB)	4	5.63
Urgent Care	3	4.23
Int Med Infect Disease	10	14.08
Ophthalmology	1	1.41
Neurology-Adult	1	1.41
Int Med Hosp Bed Specialist	3	4.23
Emergency Medicine	3	4.23
Psychiatry	1	1.41
OB/Gyn	2	2.82
Anesthesiology	1	1.41
Int Med Endocrinology	1	1.41
Age Category	**Freq**	**Percent**
20-30	1	1.41
31-40	26	36.62
41-50	24	33.8
51-60	13	18.31
61-70	6	8.45
71+	1	1.41

Table 5a: Persistence by Demographic and Clinical Characteristics

Covariates	Completed Therapy	Less than estimated Course	P-value
Gender			
Male	597 (62%)	14 (63%)	
Female	361 (37%)	8 (36%)	**p=.900**
Age			
20-40	14 (1.4%)	3 (13%)	
41-60	403 (42%)	11 (50%)	
61-80	537 (56%)	8 (36%)	
81-100	4 (.4%)	0 (0%)	**p=0.000**
State of residence			
DC	179 (18%)	1 (4.5%)	
MD	546 (56%)	14 (63%)	
VA	231 (24%)	7 (32%)	**p=.222**
Race			
API	26 (2.8%	0 (0%)	
Black	565 (61%)	14 (63%)	
Hispanic	20 (2.1%)	0 (0%)	
Multi	1 (.1%)	0 (0%)	
White	303 (33%)	8 (36%)	**p=.833**
Case Type			
Prevalent	804 (84%)	17 (77%)	
Incident	154 (16%)	5 (23%)	**p=.403**
Comorbidities			
0	284 (29%)	10 (45%)	
1	592 (62%)	11 (50%)	
2	82 (8.5%)	1 (4.5%)	**p=.261**
Insurance			
Commercial	588 (61%)	16 (72%)	
Medicare	354 (36%)	6 (27%)	
Medicaid	15 (1.5%)	0 (0%)	
Other	-	-	
Duals	1 (.1%)	0 (0%)	**p=.714**
Service Area			
BALT	133 (14%)	4 (18%)	
DCSM	586 (61%)	12 (54%)	
NOVA	238 (24%)	6 (27%)	
Network	1 (.01%)	0 (0%)	**p=.916**
Tx History			
Experienced	124 (13%)	1 (4.5%)	
Naïve	834 (87%)	21 (95%)	**p=.243**
Genotype			
1	866 (91%)	15 (68%)	
2	44 (4.6%)	0 (0%)	
3	17 (1.7%)	6 (27%)	
4	16 (1.6%)	0 (0%)	
5	-	-	
6	6 (0.6%)	1 (4.5%)	**p=0.000**

Table 5b: Persistence by Comorbid Conditions

Covariates	Completed Course	< Estimated Course	%Persistence	P-value
Stroke				
0	934	21	97.8	
1	24	1	96	0.548
Depression				
0	871	20	97.76	
1	87	2	97.75	0.999
Hypertension				
0	483	18	96.41	
1	475	4	99.16	0.004
MI				
0	932	21	97.8	
1	26	1	96.3	0.604
Diabetes				
0	726	19	97.45	
1	232	3	98.72	0.25
CHF				
0	956	22	97.75	
1	2	0	100	0.83
Smoking				
0	728	16	97.85	
1	230	6	97.46	0.723
CKD				
0	958	22	97.76	
1	0	0	0	-
ESRD				
0	958	22	97.76	
1	0	0		-
Liver Cancer				
0	924	22	97.67	
1	34	0	100	0.368
Liver Tx				
0	929	22	97.69	
1	29	0	100	0.407
SUD				
0	701	13	98.18	
1	257	9	96.62	0.142
ESLD				
0	952	21	97.84	
1	6	1	85.71	0.031
DCC				
0	952	22	97.74	
1	6	0	100	0.71
HBV Co-infection				
0	942	16	98.32	
1	22	0	100	0.541
Baseline HIV				
0	902	21	97.72	
1	56	1	98.2	0.797

Table 6a: Sustained Virologic Response (SVR) by Demographic and Clinical Characteristics

Covariate	SVR - Negative	SVR -Positive	P-Value
Gender			
Male	26 (68%)	441 (59%)	
Female	12 (31.5%)	297 (40%)	**p=.287**
Age Category			
20-40	0 (0%)	13 (1.7%)	
41-60	13 (34%)	306 (41%)	
61-80	25 (66%)	415 (56%)	
81-100	0 (0%)	4 (.5%)	**p=.589**
State of Service			
DC	11 (28%)	130 (17%)	
MD	20 (52%)	417 (56%)	
VA	7 (18%)	191 (26%)	**p=.179**
Race			
API	1 (2%)	29 (3.9%)	
Black	21 (55%)	433 (60%)	
Hispanic	0 (0%)	15 (2%)	
Multi	0 (0%)	1 (.1%)	
White	14 (36%)	235 (32%)	**p=.854**
Case Type			
Prevalent	30 (79%)	629 (85%)	
Incident	8 (21%)	109 (15%)	**p=.291**
Baseline Comorbidity (Version 2)			
0	11 (29%)	225 (30%)	
1	26 (68%)	448 (61%)	
2	1 (2.6%)	65 (8.8%)	**p=0.368**
Service Area			
BALT	3 (7.8%)	108 (14%)	
DCSM	27 (96%)	435 (58%)	
NOVA	8 (21%)	194 (26%)	
Network	0 (0%)	1 (.1%)	**p=.481**
Insurance			
Commercial	26 (68%)	442 (59%)	
Medicare	12 (31%)	282 (38%)	
Medicaid	-	-	
Other	0 (0%)	13 (1.7%)	
Duals	0 (0%)	1 (.1%)	**p=.665**
Treatment History			
Experienced	4 (10%)	98 (13%)	
Naïve	34 (89%)	640 (86%)	**p=.624**
Genotype			
1	37 (97%)	666 (91%)	
2	0	32 (4.4%)	
3	1 (3%)	14 (1.9%)	
4	0	13 (1.7%)	
5	-	-	
6	0	5 (0.6%)	**p=0.584**

Table 6b: Sustained Virologic Response (SVR) by Comorbid Conditions

Comorbid Condition	Negative	Positive	% SVR amongst patients w/ or w/o comorbidity	P-value
Stroke				
0	38	720	94.99	
1	0	18	100	0.33
Depression				
0	36	667	94.88	
1	2	71	97.26	0.37
Hypertension				
0	19	381	95.25	
1	19	357	94.95	0.845
MI				
0	38	717	94.97	
1	0	21	100	0.292
Diabetes				
0	29	561	95.08	
1	9	177	95.16	0.966
CHF				
0	38	736	95.09	
1	0	2	100	0.748
Smoking				
0	28	565	95.28	
1	10	173	94.54	0.684
CKD				
0	38	738	95.1	
1	0	0	0	
ESRD				
0	38	738	95.1	
1	0	0	0	
Liver Cancer				
0	36	716	95.21	
1	2	22	91.67	0.428
Liver Tx				
0	36	718	95.23	
1	2	20	90.91	0.355
SUD				
0	28	551	95.16	
1	10	187	94.92	0.893
ESLD				
0	38	733	95.07	
1	0	5	100	0.611
DCC				
0	38	732	95.06	
1	0	6	100	0.577
HBV Co-infection				
0	38	727	95.03	
1	0	11	100	0.448
HIV Co-Infection				
0	35	693	95.19	
1	3	45	93.75	0.654

Table 7a: Primary Cox Hazards Model (n=2962)

Covariate	Hazard Ratio	Std. Err.	p-value	95% CI
Gender	0.99	0.078	0.917	.849,1.15
Age Categories				
2	**2.014**	**0.598**	**0.018**	**1.12,3.60**
3	**2.083**	**0.625**	**0.015**	**1.15,3.75**
4	0.553	0.324	0.312	.175,1.74
Race				
Black	1.26	0.256	0.246	.850,1.88
Hispanic	1.19	0.389	0.585	.630,2.26
White	1.11	0.231	0.614	.738,1.67
State				
MD	1.14	0.119	0.182	.937,1.40
VA	0.793	0.221	0.408	.459,1.37
Service Area				
DCSM	**1.39**	**0.164**	**0.005**	**1.102,1.753**
NOVA	**1.79**	**0.513**	**0.04**	**1.02,3.14**
Network	0.655	0.659	0.675	.091,4.71
Baseline Comorbidity Count				
1	1.013	0.094	0.883	.844,1.21
2	0.888	0.095	0.271	.720,1.096
3	**0.765**	**0.116**	**0.08**	**.567,1.03**
4	0.624	0.204	0.151	.328,1.18
5	3.25	3.32	0.249	.438,24.09
6	2.19E-16	1.85E-08	1	-
Baseline Liver Complications				
1	1.169	0.185	0.324	.857,1.59
Insurance				
2	1.164	0.105	0.092	.975,1.39
3	1.32	0.434	0.384	.700,2.52
4	6.08E-16	2.96E-07	1	-
5	1.04	1.05	0.963	.145m7.54
SUD	**0.805**	**0.069**	**0.012**	**.680,.953**
HCV Tx History	0.869	0.095	0.2	.701,1.077
F-Score				
2	0.854	0.137	0.331	.623,1.17
3	0.975	0.279	0.931	.556,1.71
Case type	**3.05**	**0.376**	**0**	**2.40,3.89**
HBV Co-infection	1.208	0.346	0.508	.688,2.12
Genotype				
2	**0.699**	**0.123**	**0.042**	**.495,.987**
3	**0.607**	**0.144**	**0.036**	**.382,.967**
4	0.79	0.247	0.454	.427,1.46
5	-	-	-	-
6	0.41	0.207	0.079	.152,1.10
Baseline HIV Co-infection	1.283	0.211	0.13	.929,1.77
tvc(F-score)	0.999	0.0002	0.936	.999, 1.0004

Table 7b: Cox Hazards Model with Alternative Comorbidity Categorical Variables (n=2962)

Covariate	Hazard Ratio	Std. Err.	p-value	95% CI
Gender	0.998	0.077	0.998	.856,1.16
Age Categories				
2	**1.99**	**0.592**	**0.02**	**1.11,3.57**
3	**2.05**	**0.618**	**0.016**	**1.14,3.70**
4	0.557	0.326	0.319	.176,1.75
Race				
Black	1.27	0.257	0.238	.853,1.88
Hispanic	1.21	0.394	0.554	.640,2.29
White	1.11	0.232	0.591	.743,1.68
State				
MD	1.14	0.118	0.189	.935,1.40
VA	0.769	0.216	0.351	.443,1.335
Service Area				
DCSM	**1.39**	**0.164**	**0.005**	**1.104,1.755**
NOVA	**1.85**	**0.533**	**0.031**	**1.05,3.26**
Network	0.642	0.647	0.661	.089,4.62
Baseline Comorbidity Count				
1	0.965	0.083	0.681	.815,1.14
2+	**0.749**	**0.107**	**0.045**	**.565,.993**
Baseline Liver Complications				
1	1.167	0.184	0.327	.856,1.59
Insurance				
2	1.15	0.103	0.115	.965,1.37
3	1.34	0.438	0.369	.706,2.54
4	1.16E-17	.	.	.
5	0.977	0.982	0.982	.136,7.01
SUD	**0.796**	**0.068**	**0.008**	**.673,.942**
Tx History	0.867	0.094	0.195	.700,1.07
HBV Co-infection	1.19	0.341	0.543	.678,2.08
Genotype				
2	**0.692**	**0.122**	**0.038**	**.489,.980**
3	**0.607**	**0.144**	**0.036**	**.381,.967**
4	0.794	0.248	0.462	.429,1.46
5	-	-	-	-
6	0.418	0.211	0.085	.155,1.12
F-Score				
2	0.856	0.138	0.336	.624,1.17
3	0.975	0.279	0.93	.556,1.70
Case type	**3.02**	**0.372**	**0**	**2.37, 3.84**
Baseline HIV Co-infection	1.28	**0.214**	**0.13**	**.929,1.77**
tvc(F-score)	0.999	0.0002	0.926	.999, 1.0004

Table 7c: Sensitivity Analysis (Cox Hazards Model)– Incident Cases (n=420)

Covariate	Hazard Ratio	Std. Err.	p-value	95% CI
Gender	1.28	0.327	0.329	.777,2.11
Age Categories				
2	0.98	0.537	0.971	.334,2.87
3	1.38	0.789	0.562	.456,4.22
4	-	-	-	-
Race				
Black	0.933	1.003	0.949	.113,7.68
Hispanic	1.31	0.164	0.83	.111,15.40
White	0.716	0.774	0.758	.0806,5.96
State				
MD	0.77	0.248	0.418	.409,1.44
VA	2.31	2.25	0.389	.342,15.66
Service Area				
DCSM	1.7	0.779	0.243	.696,4.17
NOVA	0.489	0.527	0.508	.059,4.04
Network	-	-	-	-
Baseline Comorbidity Categories				
1	**0.557**	**0.148**	**0.029**	**.330,.941**
2	0.808	0.395	0.663	.309,2.10
Baseline Liver Complications				
1	1.19E-18	9.02E-10	1	-
Insurance				
2	0.929	0.279	0.807	.515,1.67
3	3.37	2.76	0.138	.676,16.81
4	-	-	-	-
5	-	-	-	-
SUD	**0.488**	**0.162**	**0.031**	**.254,.936**
HCV Tx History	1	omitted		
HBV Co-infection	1.41E-18	1.34E-09	1	-
Genotype				
2	0.952	0.656	0.944	.236,3.67
3	0.302	0.246	0.143	.061,1.49
4	0.282	0.222	0.109	.060,1.32
5	-	-	-	-
6	5.59E-13	7.53E-10	1	-
Baseline HIV Co-infection	**2.72**	**1.3**	**0.037**	**1.063, 6.95**
F-Score				
2	0.791	0.273	0.498	.402,1.55
3	0.775	0.412	633	.273,2.200
tvc(F-score)	1.0006	0.0008	0.454	.999,1.002

Table 7d: Sensitivity Analysis with Prevalent Cases (n=2542)

Covariate	Hazard Ratio	Std. Err.	p-value	95% CI
Gender	0.987	0.082	0.879	.838,1.16
Age Categories				
2	**2.903**	**1.12**	**0.006**	**1.36,6.19**
3	**2.902**	**1.12**	**0.006**	**1.35,6.21**
4	0.782	0.497	0.699	.225,2.71
Race				
Black	1.25	0.26	0.265	.839,1.88
Hispanic	1.109	0.381	0.763	.565,2.17
White	1.14	0.243	0.526	.754,1.73
State				
MD	1.19	0.131	0.115	.958,1.47
VA	0.716	0.205	0.245	.408,1.25
Service Area				
DCSM	**1.38**	**0.17**	**0.009**	**1.08,1.76**
NOVA	**2.14**	**0.625**	**0.009**	**1.21,3.79**
Network	0.62	0.624	0.636	.086,4.46
Baseline Comorbidity Count				
1	1.03	0.095	0.733	.860,1.23
2	0.787	0.119	0.115	.584,1.06
Baseline Liver Complications				
1	1.19	0.189	0.266	.874,1.62
Insurance				
2	1.14	0.108	0.158	.949,1.37
3	1.26	0.46	0.517	.620,2.58
4	0.169	-	-	-
5	0.938	0.943	0.95	.130,6.73
SUD	**0.829**	**0.074**	**0.037**	**.696,.989**
HCV Tx History	0.871	0.095	0.209	.702,1.08
HBV Co-infection	1.66	0.478	0.074	.951,2.92
Genotype				
2	0.699	0.129	0.053	.487,1.00
3	0.799	0.198	0.367	.492,1.29
4	1.09	0.374	0.795	.558,2.13
5	-	-	-	-
6	0.475	0.24	0.142	.175,1.28
Baseline HIV Co-infection	1.15	0.204	0.43	.812,1.62
F-Score				
2	0.919	0.189	0.686	.614,1.37
3	1.14	0.43	0.725	.545,2.39
tvc(F-score)	0.999	0.0002	0.569	.999,1.0004

Table 7e: MI & Smoking as Separate Indicator Variables (n=2962)

Covariate	Hazard Ratio	Std. Err.	p-value	95% CI
Gender	1.007	0.079	0.928	0.863,1.175
Age Categories				
2	**1.98**	**0.5906**	**0.021**	**1.109,3.55**
3	**2.06**	**0.6204**	**0.016**	**1.14,3.71**
4	0.569	0.333	0.337	.1802,1.796
Race				
Black	1.28	0.26	0.213	.864,1.91
Hispanic	1.23	0.401	0.517	.652,2.33
White	1.12	0.234	0.563	.750,1.69
State				
MD	1.14	0.118	0.199	.932,1.40
VA	0.748	0.213	0.309	.427,1.30
Service Area				
DCSM	**1.39**	**0.164**	**0.005**	**1.103,1.75**
NOVA	**1.9**	**0.554**	**0.028**	**1.07,3.36**
Network	0.595	0.6002	0.607	.082,4.29
MI	**0.449**	**0.098**	**0**	**.292,.692**
Smoking	0.94	0.077	0.057	.701,1.005
Baseline Comorbidity Categories				
1	1.019	0.0818	0.812	.870,1.19
2	0.983	0.209	0.939	.648,1.49
Baseline Liver Complications				
1	1.19	0.189	0.259	.876,1.63
Insurance				
2	1.14	0.104	0.131	.960,137
3	1.4	0.457	0.302	.738,2.65
4	1.85E-12	0.00001	1	-
5	1.01	1.01	0.991	.140,7.27
SUD	**0.825**	**0.072**	**0.029**	**.694,.980**
HCV Tx History	0.869	0.095	0.202	.701,1.07
F-Score				
2	0.861	0.138	0.356	.628,1.18
3	0.976	0.279	0.935	.557,1.71
HBV Co-infection	1.21	0.348	0.507	.688,2.12
Genotype				
2	**0.702**	**0.123**	**0.045**	**.498,.992**
3	**0.584**	**0.139**	**0.024**	**.367,.931**
4	0.801	0.251	0.479	.433,1.48
5	-	-	-	-
6	0.398	0.201	0.069	.147,1.07
Baseline HIV Co-infection	1.26	0.208	0.152	.916,1.75
Case type	3.01	0.37	0	2.366,3.83
tvc(F-score)	0.999	0.0002	0.895	.999,1.000

Table 8: Postestimation Statistics

Model	ll(null)	ll(model)	df	AIC	BIC
Model 1 (Comorbidity Count)	-5275.16	-5210.929	29	10479.86	10644.41
Model 2 (Comorbidity Categorical Var)	-5275.16	-5213.163	24	10474.33	10610.51
Model 3 (Incident cases)	*-381.182*	*-369.0092*	*19*	*776.0184*	*837.8116*
Model 4 (prevalent Cases)	*-4649.45*	*-4622.626*	*23*	*9291.252*	*9419.619*
Model 5 (MI, Smoking as Binary Indicator)	**-5275.16**	**-5205**	**27**	**10464.62**	**10617.82**

Aim 2: Effect of Direct-Acting Antiviral Treatment for Chronic Hepatitis C on Healthcare Resource Utilization

Introduction:

Randomized clinical trials for direct-acting antivirals (DAA) have demonstrated cure rates of over 95%. [28] These cures for chronic HCV have been hailed as medical breakthroughs given that HCV is infectious and leads to burdensome advanced liver disease. However, these prescription drugs have been exorbitantly priced – given investments required to develop drugs, manufacturers have justified prices ranging from $26,000 to $100,000 per course of therapy. This tension raises the question – are the new treatments worth the price? In addition to the inherent benefits of a cure, there may be spillover effects that should be considered when assessing the value of these drugs.

The appropriate use of prescription drugs can offset future resource utilization in many chronic conditions – by properly managing a disease with medication, it reduces the need for unexpected, often expensive, resources. The most clinically and economically burdensome stages of HCV include liver cancer, end-stage liver disease and liver transplants. These severe sequelae eventually develop in about 20% of infected patients if the chronic HCV is not treated. DAAs can successfully cure the infection and reduce the risk of developing advanced liver disease – prevention of these advance manifestations are tangible spillover effects that should be considered when measuring the value of DAAs. Although public and private payers may negotiate lower prices for their beneficiaries, these drugs still place a great financial burden on health plans and, subsequently, patients. Pharmaceutical manufacturers justify these price tags with the potential for long-term savings, however high drug prices may minimize these gains.

This study aims to provide an estimate of the effect of DAA treatment for chronic HCV on healthcare resource utilization after treatment completion. We will explore this relationship among HCV patients who received care from a Kaiser Permanente Mid-Atlantic States (KPMAS) health care provider. As more patients become eligible for treatment with more systematic screening practices, it is important to understand the clinical and economic implications of making this large investment to cure this infectious disease.

Conceptual Framework:

Lipton and Bird first proposed a framework (Figure 1) to evaluate drug utilization review programs. They described factors, across multiple domains, which influence prescribing practices, variation in which subsequently impacts healthcare resource utilization. We adopted this framework to our study setting, KPMAS, by including specific information about this health system.

Health system factors create an environment in which clinical decision-making, or provider prescribing, occurs. Many of these system factors construct the boundaries within which providers must practice and often influence prescribing decisions. The providers in this study are subject to the healthcare policies set up by KPMAS. These include the drug formularies that indicate which of the DAAs are preferred, the way in which care is coordinated within the health system and how provider practices are set up within KPMAS. Providers may also take into consideration treatment guidelines outlined by national societies such as the American Association for the Study of Liver Diseases (AASLD). While providers are encouraged to follow these guidelines, the environment in which they practice and the types of patients they see may lead them to adopt an alternate treatment route better suited for the patient. If variation across patients could motivate deviations from evidence-based practice guidelines, it is important to understand the implications of these influences on patient outcomes.

A patient's magnitude of resource use is driven by the severity of the condition once diagnosed with a specific disease – for example, patients with decompensated cirrhosis have greater recourse use than patients who have not yet developed cirrhosis. [42, 155] Other patient-specific characteristics, the delivery system in which the patient receives care, the patient's insurance coverage and the specialty of the provider they see can impact the magnitude of resource use. Further, the course of treatment the physician takes can alter the amount of resource use such as hospital visits. [156-160] In addition to treating the present condition, a positive externality is often a reduction in the amount of medical care the patient requires in the future. This framework provides a way to conceptualize and quantify the relationships described here within the context chronic HCV. While the opponents of the significantly high prices highlight the ethical and economic issues created by the cost of these drugs, the proponents tout the potential downstream offsets when patients are treated today. [96, 161, 162]

Previously published work has assessed this association between drug treatment and subsequent healthcare use in a variety of conditions including cardiovascular disease, diabetes and HIV. [159, 160, 163-165] Majority of the

literature in the HCV space has looked at this particular question in the older generation drugs. [166] Given the improvement in efficacy and reduction in side effects of the second-generation DAAs, it is hypothesized that more patients will be successfully cured and therefore can experience greater resource use offsets in the long-term. [28]

Objective & Hypotheses:

The objective of this analysis was to compare healthcare resource utilization, for chronic HCV patients who were treated with new DAA therapies versus those who did not receive therapy, after treatment completion. This analysis tested the following null hypothesis: rates of total (ambulatory, emergency department, and inpatient) resource utilization for HCV patients will not differ significantly in the follow-up period after treatment completion.

Data:

We used both administrative claims and electronic health records (EHR) from KPMAS to conduct this study. KPMAS is an integrated healthcare system that serves over 700,000 individuals in Maryland, Virginia and the District of Columbia. KPMAS includes both private and public insurance programs. The demographics of KPMAS' enrollees closely match those of the population of its service area. As of January 2017, the population demographics were the following: 53% female, 40% non-Hispanic Black, 35% non-Hispanic White, 12% Hispanic and 10% Asian/Pacific Islander. The KPMAS data repository included 100% of administrative claims and greater than 90% of all patient prescriptions. Lab and diagnostic results, outpatient visits, urgent care visits and procedures were captured in an EHR.

KP HealthConnect, the KPMAS EHR system, provides patients and providers an opportunity to coordinate care. It links important information like details about recent provider visits or hospitalizations, lab test results, prescription fills, procedures, health insurance data and billing information. KP HealthConnect was the source of our patient-level clinical data. We pulled patient demographic information, patients' clinical histories, lab test results, procedure information, insurance information and prescription records. Dates of diagnosis, enrollment in the KP health plan, and treatment were all extracted to use in the construction of the study cohort and outcome variables.

KPMAS has an established Hepatitis C Registry, which identifies current and historic patients with HCV using hierarchical criteria (Table 1). The most specific criteria is that of HCV RNA tests, which accounts for >60%

of the registry. This registry allowed us to identify the population of interest and gather data to observe patients with chronic HCV over the course of the disease and treatment process.

Study Periods of Assessment:

We assessed all independent covariates of interest during the 12 months prior to the study start date, beginning November 1, 2012, and these were labeled as the baseline covariate values. We enumerated the encounters during this baseline period to provide a baseline metric of use for patients in preparation for the propensity score analysis. By adjusting for this, we can achieve greater balance across comparison groups. Further detail can be found in the statistical analysis section below.

Patients could then be treated during the study period that began on November 1, 2013 and ended on May 31, 2016. Given the economic outcome of interest, we imposed a minimum follow-up period of at least 6 months after the treatment regimen stop date. Much of the literature states that offsets of the new DAAs will accrue in the long-term – when the more severe stages of chronic HCV are prevented. [101, 109, 167] However, since our study period was short given availability of patient data, we had to balance sample size and follow-up period to maximize our ability to detect any meaningful difference between the treated and untreated patients in the outcome period.

Figure 4 illustrates the details of study period for the analytic approach taken in this study. This is described further in the Analysis sections below.

Encounter Data:

The encounter data, or visit data, was extracted from the EHR data at KPMAS. Encounters were pulled and classified as baseline, if they occurred within the year prior to 11/1/2013. Follow-up began on November 1, 2013 – post-treatment periods began in the interval after treatment completion (Figure 4). We used the baseline count of encounters as a baseline metric of utilization – to control or account for patients who were already considered heavy users of healthcare resources, regardless of HCV status.

There were nine unique types of encounters patients could experience. Inpatient encounters included acute inpatient hospital stays, same day hospital discharges, hospital transfer when patients were admitted to the hospital, acute inpatient psychiatric stays and detox stays. Emergency department encounters excluded urgent care visits.

Ambulatory encounters included outpatient clinic visits, same-day surgeries, observation beds, urgent care visits and same-day ambulatory hospital visits. These excluded emergency department visits. Patients could also have telephone or e-mail encounters with a KPMAS physician. Non-acute institutional stays included hospice, skilled nursing facilities, rehab, nursing home stays, residential stays, overnight non-hospital dialysis and other non-hospital stays. "Other encounters" included non-overnight hospice visits, home health visits, skilled nursing facility visits or other visits that did not occur in a typical ambulatory clinic or hospital setting. A lab only encounter included an encounter that is not associated with any other type of visit – if a patient only had to come into a facility to have laboratory tests performed. Finally, a radiology only encounter included an encounter that is not associated with any type of visit – if a patient only came in to a facility to have a radiology exam conducted.

For this study, we focused on total, ambulatory (AV), emergency department (ED) and inpatient (IP) encounters. In addition to consistency with the types of encounters assessed in the current literature, we focused on these three specific types of encounters because they comprise the majority of the economic burden for chronic HCV.

Statistical Analysis

We followed a retrospective observational cohort of chronic Hepatitis C patients at KPMAS and observed DAA regimen initiation, or lack thereof, which occurred. Treatment was not randomly assigned in our study sample and so we used propensity scores to balance the patients who were and were not treated on possible confounding factors. Propensity score matching has been used in previously published work to evaluate the effect of a treatment, specifically a prescription drug, on post-treatment resource utilization using observational patient data. [168-172]

We then used a panel data analytic approach to determine the effect of treatment on resource utilization (total, ambulatory, emergency department and inpatient). Briefly, we conducted a longitudinal analysis to determine the effect of treatment on the rate of resource use for patients with chronic Hepatitis C after treatment completion.

We provide more details on these methodological steps below.

Steps for Propensity Scores:

Propensity Score Models:

We used propensity score matching in this study because it allows for better control for these variables than simply including them as covariates in the outcome model. We used logistic regression to estimate propensity scores for each patient in the model. The equation below shows the general structure of the regression analysis:

$$\ln (PS/(1-PS)) = \beta_0 + \beta_1 X_1 + \beta_2 X_2 + \ldots + \beta_{p-1} X_{p-1} + \beta_p X_p$$

We included covariates in the propensity score model that could potentially influence treatment. Some of these covariates were found to be significant predictors of the risk of treatment in the survival analysis we conducted in a prior analysis. Others have been hypothesized to influence utilization in the literature. Lipton and Bird, as discussed above, provided a conceptual framework for evaluating downstream effects of medication decisions. All of these characteristics – patient, provider or system – were determined at baseline.

Covariates Included in the Propensity Score Model

The main demographic covariates included in the propensity score model were gender, race and age. KPMAS provided reported and imputed data on its members' racial, geographic and socioeconomic characteristics. This resource allowed for more complete data on important characteristics of the patients in our study cohort. Gender was a categorical variable and indicated either male or female and age was a continuous variable operationalized as the age-at-entry of the study. Race was self-reported and categorized as: Asian-Pacific Islander, Black, Hispanic, Multiracial or White.

Geographic characteristics included state of residence and healthcare service area. State indicated which of the three states, Maryland, Virginia or Washington D.C., the patient resides. Service area indicated, at a more specific level, where they were receiving care from their primary care physician, or was suggestive of a proxy for a patient's medical home. This information is also of particular importance when comparing patients covered under Medicaid since the reimbursement rules differ across states for certain Hepatitis C drugs. Service area, where in the KPMAS network the patient sought care, included the Baltimore area (BALT), District of Columbia/Suburban Maryland (DC/SM) and Northern Virginia (NOVA).

Insurance type was a categorical variable with patients classified as having commercial, Medicare, Medicaid, dual-eligible and other. The original data collected from the health records indicated if a patient had any one of these types of insurance coverage at any time over the course of the study period. It follows that multiple payers covered some patients during the study. We narrowed the categories down to the four types of payers by creating a hierarchy of how certain payers take precedence over others. Specifically, if a patient had Medicare at any time, they were classified as having Medicare. If a patient had Medicaid at any time, they were classified as having Medicaid. If a patient had Medicare and Medicaid, they were categorized as dual eligibles since this is a unique population.

The comorbidities were identified using a combination of diagnosis, medication and laboratory data. For the majority of these comorbidities, we were interested in knowing and including in our analysis whether or not the patient had a history of a certain condition or already had a confirmed diagnosis at baseline. Not all of these comorbidities were found to be significantly predictive of treatment in the previous analysis, but may still impact utilization for the patient down the road. Further, we aimed to control for these potential confounders, as they might differentially impact resource utilization depending upon treatment status. We defined a baseline comorbidity as having the specific diagnosis or procedure code prior to the two-week buffer before the baseline date (baseline minimum date). A history of or prior diagnosis of a given comorbidity may impact the progression of the HCV infection, subsequently impacting the decision to initiate medication and thereby influencing utilization into the future. Stroke, congestive heart failure, depression, hypertension, myocardial infarction and liver cancer were all identified using their diagnosis codes prior to the baseline minimum date.

We used medication data to identify diabetes status, HBsAG and HBV DNA results to identify hepatitis B co-infection, and EHR transplant dates to identify patients who have had a prior liver transplant. Smoking is identified via self-report at KPMAS and baseline status was defined as either smokers as of the baseline date or no history of smoking. Patients were either identified as being treatment experienced or naïve, which was determined using prescription records and medication codes prior to the baseline minimum date. Treatment history has been discussed in the literature as impacting future treatment success or treatment initiation thereby having an effect on downstream healthcare resource use. [124, 125]

We also had diagnosis data on liver-related complications. Patients could develop decompensated cirrhosis or end stage liver disease before or after the baseline date. The presence of chronic kidney disease was identified from KPMAS' CKD registry. Patients could develop the condition during the study period or have a history of CKD. We operationalized end-stage renal disease in the same way.

We also included a covariate that indicated the presence of a substance use disorder (SUD) that was operationalized as the number of encounters for an SUD based on ICD-9-CM diagnosis codes. If a patient had any non-zero number of encounters, we considered the patient to have a confirmed diagnosis of a substance use disorder. There is some discussion in the literature surrounding the higher likelihood of the chronic infection as a result of drug or alcohol abuse. [1] Further, in our previous analysis, we found the presence of SUD to be a significant predictor of the risk of treatment and so included it as a separate covariate in the propensity score model.

We constructed a composite measure based on the count of the comorbidities collected for this study. This was operationalized as a categorical variable: 0 comorbidities, 1-2 comorbidities or greater than or equal to 3 comorbidities. Specifically, we only included comorbid conditions that are most common to, or most likely to be experienced by, HCV-infected patients. These include stroke, congestive heart failure, depression, hypertension, myocardial infarction, smoking, diabetes, chronic kidney disease and end-stage renal disease.

We also included baseline Hepatitis B and HIV status in the propensity score model. HBV/HCV and HIV/HCV co-infected patients are unique in the way the disease manifests in patients given the toll on a patient's immune system. [1] The co-infections may influence the therapeutic regimen of choice given drug interactions as well.

Finally, we included a measure of baseline healthcare resource utilization in the propensity score model as one of the determinants of probability of treatment. In this way, we can control for especially high or low healthcare users at baseline. By adjusting for this baseline characteristic, we can better identify the effect of the drug treatment regimen itself on post-treatment utilization and minimize confounding. This measure was a simple count of encounters prior to November 1, 2013, or the study start date.

Implementation of Propensity Score Model

When estimating the propensity scores, we implemented certain diagnostic tools to assess the balance of the propensity scores calculated. In constructing the sample, from which we would conduct matching, we calculated

a range of scores over which we could find patients in either the treated or untreated groups. This excluded patients with propensity scores that were too extreme – either too large or too small. By doing so, we ensured, that for each value of each of the covariates we included in the propensity score model, there was some positive probability of belonging to both treatment groups.

We also assessed balance across treatment groups using standardized bias. [173] Standardized bias for continuous covariates is the difference in means between the two groups divided by the standard deviation. For categorical variables, it is the differences in proportion at each level of the covariate. [173] We estimated standardized mean differences in the covariates before and after matching patients on propensity scores.

After we determined the sample of patients who fell within the range of common support, the matching algorithm then matched patients in the 'treatment' group to patients in the 'no treatment' group. We conducted nearest neighbor matching with a 2:1 ratio.

Statistical Analysis – Outcome Model:

Interval Utilization Counts

While all covariates were determined at baseline, patients in our study sample could have been treated at various times over the course of the study period between November 1, 2013 and December 1, 2015. Although we imposed a six-month minimum follow-up time, ensuring all patients had completed their treatment regimen by December 1, 2015, patients treated earlier during the study period would have more follow-up time than those treated immediately before the 12/1/2015 cut-off.

To take advantage of this varying amount of follow-up and better approximate the post-treatment period for each treated patient, we divided the study period into six-month intervals and calculated use in each interval. Figure 4 illustrates the setup of the panel data set and identifies each of the intervals over the course of the study period. The counts of encounters (all, ambulatory, emergency department and inpatient) are repeated measures of the outcome over time. Specifically, we divided the study period from November 1, 2013 to December 1, 2015 into four intervals as follows: 1) November 1, 2013 to May 1, 2014; 2) May 1, 2014 to November 1, 2014, 3) November 1, 2014 to May 1, 2015 and 4) May 1, 2015 to December 1, 2015. The baseline period, during which the values of the independent variables were measured, was the one-year period prior to November 1, 2013 – between 11/1/2012 and

11/1/2013. The last six months of the observational period, between December 1, 2015 and May 31, 2016, was the final utilization interval. Resource utilization counts were estimated in a similar manner for patients who never received treatment during our study period. Using the treatment regimen dates, we created variables to indicate the interval during which a patient was treated. These interval utilization counts served as the outcome – measures of resource use over time - for the panel data analysis described below. For treated patients, the outcome measures of resource use are those after the treatment was completed – or after the interval during which treatment took place.

Panel Data Analysis

After constructing utilization counts, for each of the different types of encounters, in each of the six time periods, we created a panel data set in order to assess the effect of treatment on resource use. We had repeated utilization measurements for each patient over the course of 6 six-month periods. Using the interval-specific treatment variable created above, we converted the treatment status variable to a time-varying indicator of treatment status. The value of this variable was 0 when patients were not treated and turned to one during the interval when patients were treated. After treatment, this variable remained turned to 1 in each of the subsequent study intervals. In this way, once a patient was treated with a DAA, all subsequent intervals were their 'post-treatment' period. All other independent variables were measured at baseline and did not change over the course of the study period. We also included binary variables that each indicated whether or not the patient was treated in that interval. In this way, we captured a potential effect of the time of treatment, during our particular study period, on post-treatment utilization. We only assessed treatment after Interval 0 and so we did not include a variable for this particular interval. Additionally, given that we only included patients who were treated through December 1, 2015, no patients in our sample were allowed to initiate treatment in Interval 5 – we did not include a variable for Interval 5.

We used a negative binomial regression model to estimate the effect of treatment on the outcome – counts of different types of resource utilization (number of all encounters, number of ambulatory encounters, number of inpatient encounters and number of emergency department encounters). We conducted the longitudinal equivalent of a negative binomial regression model while accounting for repeated measures of resource use within each panel (or unique patient) in our sample.

We fit random-effects overdispersion models and population-averaged negative binomial models to our data. The random effects model for count data, using the 'xtnbreg' specification in STATA, is the random intercept model for longitudinal count data. For the panel data analysis specific to count outcomes, the random-effects and fixed-effects specification refer to the dispersion across panel variables. In our case, the panel variable is the study identification number that uniquely identifies a patient in our sample. While the fixed-effects model would indicate that the dispersion is the same across all patients, the random-effects model allows the dispersion to vary randomly from patient to patient – the inverse of 1 plus the dispersion follows a Beta(r, s) distribution (Tables 8-9). The likelihood ratio test, included in the output of this model, provides evidence as to whether or not the random intercept is necessary. [174, 175] A significant result in this test indicates that the random effects 'xtnbreg' specification is more appropriate than the fixed effects option – whether a random intercept model or a pooled estimator is a better fit. Given the variability in the timing of treatment (Table 6) and the range of pre-treatment utilization counts, we hypothesized that the random-effects specification would be more appropriate and a likelihood ratio test would test this hypothesis.

We also estimated a population-averaged model with an autoregressive correlation structure (order 1) since it is reasonable to assume that resource utilization in the first six-month interval may influence the utilization in the second six-month interval. The population-averaged model makes the assumption that there is no panel specific intercept – the dispersion does not vary from panel to panel (patient to patient).

The results for all of these models were interpreted as incidence rate ratios – comparing the rate of a particular type of resource utilization between those who were treated and those that were not.

Adjusted All Encounters

We conducted the 'All Encounters' analysis on adjusted overall encounters. As described in previous sections, we know that the resource burden associated with an inpatient encounter is much greater than that associated with an outpatient, or AV, encounter. The average expense per inpatient day is about $2,271 (2012) [176] and the average length of stay is about 4.5 days [177] – for a total average cost of an inpatient stay of approximately $10,219. The average cost of an emergency room visit is approximately $1,233. [178] Outpatient encounters can occur in an office ($199), hospital setting ($1,275) or in an emergency setting ($922). [179] Since outpatient visits could

occur in a physician's office or in Kaiser's clinical decision units – an alternative option to the traditional emergency room – we took the average of these costs for an approximate cost of $798 (2011). After adjusting these costs for inflation to 2016 U.S. dollars, we found the following: $10,933 for an inpatient stay, $1,326 for an average emergency room visit and $858 for an average outpatient visit.

We adjusted the overall encounter count based on a ratio (12.75:1:1.5) of the average costs of each type of encounters from a national perspective. [177, 178, 180] For example, if a patient had a total of 5 encounters – 2 inpatient, 1 ambulatory, and 2 emergency department – this patient would actually have a total of 28 encounters all equivalent to the resource burden of an ambulatory encounter. The adjustment yields the following: 24 inpatient, 1 ambulatory, and 3 emergency department encounters. In this manner, we are weighting the more resource heavy encounters, IP and emergency department, to create more comparable outcomes for the "all encounters" analysis. Any regression results on the 'All Encounters' outcome was conducted on these resource-adjusted encounters.

While the 'All Encounters' analysis provides an aggregate picture of resource utilization, results on specific encounter types can be more actionable from a health system or payer perspective.

Results

Sample Size

After imposing the minimum follow-up criteria of six months of follow-up time after treatment completion, 2,533 patients remained in the sample. Prior to propensity score matching, 603 of these patients were treated and 1,930 were not treated. Those 603 treated patients had a therapy regimen stop date prior to December 1, 2015.

Table 2 shows the sample size requirements per group in order to detect a given effect size in a comparison of means between two groups. The final matched sample, described more below, included 449 treated patients with the six-month follow-up period for outcome assessment (December 2015 to May 2016). We were still able to detect a 20% effect size with the 2:1 matching algorithm we conducted.

Description of Encounters

In the entire study sample, there were a total of 97,438 unique encounters that occurred. Within these encounters, the number of services provided or procedures performed varied. Majority of the encounters were AV

(93.22%) while ED and IP encounters each made up only a little more than 3% of all encounters. Table 3 shows the distribution of each of these encounter types by treatment status and by the time period in the study during which the encounter occurred.

Assessment of Propensity Score Matching

Table 4 compares the distribution of the patient characteristics in the total unmatched sample and the matched sample included in the utilization regression analysis. The distribution of age, service area, genotype and comorbidity count were significantly different prior to running the propensity score matching but these significant differences were no longer present after propensity score matching.

Figure 5 shows the distribution of the propensity scores for both the untreated and treated patients. In an ideal scenario, the red and blue histograms (Figure 5) would mirror each other and would indicate that at each propensity score there are an equal number of patients in the untreated and treated group. Patients may drop out of the sample if they have extreme propensity score values – on the low or high end – and there is no counterpart with a similar propensity score the other group. There were 1,566 patients that fell within the range of common support and were available for matching. After implementing the nearest neighbor 2:1 matching algorithm, we had a total of 1,347 patients (449 treated) in the analytic sample.

Table 5 provides the results of the 'pstest' in STATA – it shows the percent reduction in standardized bias from the unmatched sample to the matched sample. Figure 6 illustrates these quantitative results. In general, a good match will have achieved less than 5% bias. [170, 181-183]

For the following covariates, we find a successful reduction in standardized bias: service area, race, baseline F score, baseline comorbid count, baseline liver complications, baseline presence of substance use disorder, patient state of residence, treatment history and HCV genotype. We found the bias was substantially reduced to below five percent for each of these covariates. However, we did see a slight increase in percent bias in the following covariates: age (5.7% to 7.8%), gender (4.7 to 5.8%), insurance status (-0.7 to -2.5%), baseline hepatitis B co-infection (5.3% to 7.7%), baseline HIV co-infection (0.4% to -1%), and baseline use (3.1% to 3.3%). Insurance status, baseline HIV co-infection and baseline use still had less than 5% bias across the two treatment groups in the

matched sample. Age, gender and baseline hepatitis B co-infection had between 5% and 8% bias in the matched sample. It should be noted that the bias was small in these covariates even prior to matching.

The t-tests associated with each of these comparisons tests the null hypothesis that the mean values of the two groups do not differ after matching – the p-values for each of these tests on each covariate are greater than .05 and therefore the null cannot be rejected.

Table 4 further demonstrates that the distributions of covariates across treatment groups – in the matched sample – are not statistically significant.

Overall, in the matched sample, the mean bias reduced from 7.7% to 3.5% and the median bias reduced from 5.6% to 3.3%. With both of these summary measures below 5%, we feel comfortable with the match.

Panel Data Analysis – Time-Varying Treatment

Unadjusted Summary Statistics

About 12% of patients were treated in either quarter one or quarter two – between November 1, 2013 and November 1, 2014. Just under 50% of treated patients received treatment in quarter three, between 11/1/2014 and 5/1/2015, and about 38% were treated in interval four between 5/1/2015 and 12/1/2015 (Table 6).

Table 7 provides mean and median resource utilization per interval for each type of encounter. The 'N' shows the number of patients in each interval that belonged to each group – treated if they were treated in that interval or before and untreated if they were still not treated. In this way we capture the time-varying nature of treatment. We see a few patterns emerge in these unadjusted exploratory estimations. For those treated earlier, in intervals 1 or 2, we see on average, more use in those patients who remain untreated than those who are treated. As we move on to the later intervals, we see on average, more use in those patients who were treated than those who remained untreated. Absolute magnitude of inpatient and emergency department encounters is less than 1 and the differences are even less than 0.5 – the results of the adjusted analyses, discussed below, will provide more information.

Adjusted Regression Model Results

We examined all encounter outcomes in the time series analysis – including all, AV, ED and IP. We determined that the random effects model was the most appropriate. The likelihood ratio test showed the random effects model, allowing for varying dispersion across each patient, was the best fit to our data. Given the variation in the range of number of encounters per person and utilization at baseline, or interval zero, this result makes sense. We do present some results, for comparison purposes, of the population average model with an autoregressive correlation structure.

We found a downward effect of treatment on resource utilization – the anticipated direction given previous studies and clinical trial results. Patients who were treated experienced lower rates of all types of utilization, however these results were not statistically significant. The effect of treatment on use is labeled as "Tx" in the regression models (Tables 8,9). For example, we found that if a patient were treated, they experienced a reduction in their rate of 'all encounter' utilization of about 10% (IRR: 0.909, 95% CI: 0.760, 1.059) (Table 8). We found a similar magnitude of treatment effect for ambulatory encounters (IRR: 0.887, 95% CI: 0.740, 1.038) (Table 8)

We also found some differences in resource utilization based on the timing of treatment. Specifically, those patients treated in interval 1, in comparison to those that were not, had fewer ambulatory encounters while those treated in any of the later intervals had greater ambulatory resource use. Only treatment during interval 3 was significantly associated with resource utilization in the ambulatory encounter model (Table 8) Treatment timing was not significant in the all encounters model. There are some possible explanations for this difference. Patients treated earlier had a longer follow-up during which we were able to observe resource use after treatment and so there was more opportunity for us to see any magnitude of reduction. Patients treated later may have developed more severe illness by the time they were treated and so were using more ambulatory resources.

Patients also experienced a reduction in the rates of ED and IP encounters. Holding all other covariates constant, treated patients experienced a reduction of about 30% in their rate of emergency department encounters, however this was not statistically significant (IRR: 0.705, 95% CI: 0.358, 1.052) (Table 8). Again, only treatment during interval 3 was significant (IRR: 1.41, 95% CI: 1.102, 1.804) – leading to increased post-treatment emergency department utilization (Table 8). We found that treated patients experienced a reduction in inpatient encounters of about 19% (IRR: 0.811, 95% CI: 0.595, 1.026) (Table 8), holding all other characteristics constant, although this

was not statistically significant. Treatment timing, during any interval, was not significant in the inpatient models. We found a similar pattern in both ED and IP encounters as we saw above - the IRR increases with later treatment intervals.

Population Average Model

Results of the panel data analysis with an autoregressive correlation structure (order 1) were similar (Table 9) – this specification showed a downward effect of treatment on the rate of resource utilization, but none showed significant effects.

The magnitude of the effect on all and ambulatory encounters, although insignificant, is much smaller than those found in the random intercept specifications described above (Table 9). In the all encounters model, treatment during interval 1 was significantly associated with a reduced rate of subsequent resource utilization (IRR: 0.441, 95% CI: 0.2996, 0.6490). Treatment during interval 4 was also significantly associated with increased post-treatment utilization (IRR: 1.134, 95% CI: 1.043, 1.234). This follows a similar pattern that we found in the models described above. In the ambulatory encounter model, treatment during interval 2 was significantly associated with decreased post-treatment utilization (Table 9)

We found that treatment also reduced post-treatment emergency department and inpatient utilization, however, these results were not statistically significant (Table 9). We found a similar pattern with the treatment interval variables in the inpatient model where treatment in later intervals was associated with increased subsequent resource utilization and earlier treatment was associated with decreased utilization. This pattern deviated slightly in the emergency department model (Table 9).

Strengths & Limitations:

While we saw a reduction in the rate of resource use for patients treated with DAAs for all types of encounters, we did not find these effects to be statistically significant. There are both strengths and limitations of this analysis that may provide some reasoning behind our findings.

We had access to data from KPMAS' electronic health record data, which provides patients and providers an opportunity to coordinate care. It's links between provider visits, hospitalizations, lab test results, prescription

fills and billing information were critical in assessing associations between patient and provider characteristics and healthcare resource utilization.

We previously conducted a survival analysis to determine predictors of DAA treatment in the same study sample used in this analysis. We did not find the time-varying covariate, the F-score, to significantly change the likelihood of treatment over time. We therefore felt comfortable in our assumption that the likelihood of treatment was determined by the baseline measurements of covariates. Further, since the treatment in this observational study was not randomly assigned, using propensity score matching was the right approach to construct similar treated and control groups for this analysis. We achieved a reduction in standardized bias between the groups for the majority of the covariates of interest. While the standardized bias slightly increased for some covariates, the percentage bias remained under 8%.

We imposed a minimum of six months follow-up for treated patients – the treatment regimen had to be complete by 12/1/2015 – in an effort to adequately capture resource use in the post-treatment period. However, this follow-up time was likely not long enough to capture the general clinical progression of disease or to see any substantial effect of treatment on resource use. Previous studies, asking research questions in the interferon-era, have followed patients over the course of years to measure the effect of HCV treatment on resource use. [112-114] This limitation is important to consider when interpreting the statistically insignificant results. Future research should include prospective studies with long-term follow-up to better capture the possible downstream resource offsets from DAA therapy. Majority of the encounters, or resource use, in our study period included ambulatory visits. A longer follow-up time may allow us to capture more inpatient or emergency use, or offsets, after treatment.

The panel data analysis was a strong methodological approach as it reflected the time-varying nature of treatment over the course of our study period. This approach addressed the fact that if a patient was treated in interval one, they had more than a year of additional follow-up than a patient who was treated in interval four – by accounting for these differences, our definitions of pre-treatment study time and post-treatment study time appropriately represented what happened to our sample over the study. We found that only a small proportion of the treated group received treatment in the first or second intervals (~9%) and most of the treated patients completed therapy during the third or fourth intervals (~91%). Using a time-varying treatment indicator in the panel data captured this variability in ‘pre’ and ‘post’ treatment duration.

With any count data, overdispersion must always be considered and the negative binomial model, as opposed to the poisson model, addresses this issue. Further, the random intercept model – or random effects *xtnbreg* specification – allowed for the dispersion to vary across patients in our study sample and accounted for the repeated measures aspect of our data.

It should also be highlighted that there was a clear increase in the number of treated patients beginning in November of 2014. Harvoni, Gilead's second drug, was approved in November of 2014 and the majority of patients at KPMAS, at the time of the study, were being treated with Harvoni. The largest portion of the study sample was treated after November 2014. Since we required treated patients to have completed therapy by December 2015, our study sample included mostly patients treated during this one-year period. Only about 9% of the treated patients initiated therapy between November 2013 and November 2014 – during either interval one or two (Figure 5). This increase in treated patients, after the approval of Harvoni, combined with the six-month follow-up criteria, limited the sample size. With the evolving DAA market, it is important to capture the role of timing of treatment for HCV.

The use of observational data in determining a treatment effect is always subject to some unobservable confounding. While we used a propensity score matching approach to account for the nonrandomized assignment of DAA treatment, there may have been some unaccounted for factor, or immeasurable characteristic, that impacted treatment initiation for a particular patient. For example, a provider's perception of a patient's ability to comply with the required therapy, specifically amongst patients with substance use disorders, may influence treatment initiation. However, we are not able to quantitatively measure a provider's perception of their patient and so we rely on diagnosis data, of a substance use disorder, in this particular case.

Measuring outcomes after treatment in a real-world population is an important step in determining the effectiveness of a drug, which provides a sense of how the newly developed therapies will work outside of a clinical trial setting. The data from KPMAS provided an ideal environment in which to observe the use of these new drugs in a real-world environment, however, the generalizability of the study is limited. The structure of this particular integrated system and the care pathway for HCV patients in this region of Kaiser Permanente may not only differ from other Kaiser systems but from other health care systems, integrated or not, as well. For example, there are a series of important tasks carried out by HCV Care coordinators by continually engaging patients along the care pathway. [133] This resource may not be available in other care settings.

Policy Implications & Discussion:

This study is timely given the recent approval of multiple DAA treatments for chronic HCV. As we move towards healthcare delivery focused on assessing and delivering value-based care, it is imperative to understand the potential clinical and economic benefits of breakthrough discoveries such as DAAs. The high price tags of these curative therapies warrant the assessment of the potential downstream effects on resource utilization to determine the possible offsets of the initial investment. Our study assesses the short-term resource use after DAA treatment. Although our results were not statistically significant, we did find that DAA treatment has the potential to reduce resource utilization in the post-treatment period. Further, we found that timing of treatment, which has recently varied across care settings given the drug prices, also has some effects on resource utilization. We discuss the implications of these findings in the context of the value of these pharmaceutical products.

Our results follow consistently from the results of clinical trials and the current literature on first-generation and interferon-based regimens – treatment with DAAs reduced subsequent healthcare resource use. We also found that earlier treatment was associated with a reduced rate of post-treatment resource utilization, while those treated earlier experienced increases rates. Although these were not significant results, they provide some support of the clinical arguments in favor of earlier treatment. [3]

Similar to the evidence on the reduction in risk of CKD, two recent studies conducted in the Veteran's Affairs population in the United States have shown a marked reduction in risk of liver cancer after successful treatment with second-generation DAAs. [184, 185] Kanwal et al. found that patients successfully treated with DAAs experienced a 72% (HR: 0.28, 95% CI: 0.22, 0.36) reduction in the risk of developing HCC. Ioannou et al. found a significant reduction of similar magnitude. At the same time, they both found that patients who had already developed cirrhosis had the highest annual incidence rate of HCC even after cure. [184, 185] It follows that if treated earlier, patients can reduce their risk of advanced extra-hepatic manifestations that require substantial healthcare resource use. Further, similar to our study, both research teams noted a short follow-up time as a limitation of their analyses. It is imperative that HCV patients with advanced liver disease, or cirrhosis, continue to be monitored for HCC even after DAA therapy is completed – currently, KPMAS does conduct annual liver cancer screening even after a patient has completed DAA therapy to monitor patients for this possibility. [133]

Another recent study looked at the impact of HCV cure on glycemic control in patients with diabetes. Using a sample of diabetic HCV-infected patients in the Veterans Affairs healthcare system, Hum et al. measured hemoglobin A_{1c} levels and use of antidiabetic medications before and after DAA therapy. [186] Patients who were successfully treated experienced a greater reduction in HbA_{1c} and reduction in use of antidiabetic medication than those who failed therapy. Specifically, while those who achieved cure experienced a drop in the use of insulin, from 41.3% to 38%, those who failed therapy experienced an increase from 49.8% to 51%. [186] While the results from this study are promising for a population in which HCV is highly prevalent, Hum et al. did not measure the resource outcomes we examined. For example, with better glycemic control, do patients require fewer visits to their primary care physician or fewer unexpected hospital admissions due to diabetic complications? Hum et al.'s post-treatment period included 12 months of follow-up after treatment completion for all patients in the study sample – in our panel data analysis, majority of the patients had between 6 months to a year of follow-up. With longer follow-up, we can determine if short-term endpoints have a lasting effect.

Studies examining treatment effect in the second-generation DAA era are limited due to the recency of the drug approvals and short follow-up periods. Published evidence on the effect of treatment on resource utilization exists, however, this literature focuses on the previous standard of care. While interpreting our results in the context of these studies, readers should keep in mind that these therapies differ in effectiveness, the presence of side effects, length of treatment, difficulty of administration and cost. Further, the analyses benefit from longer post-treatment periods since these drugs have been in use for a greater amount of time.

Manos et al. explored differences in utilization by treatment status for patients taking interferon and ribavirin therapies in the Kaiser Permanente Viral Hepatitis Registry in northern California. This group of researchers had five years of total follow-up with a mean duration of post-treatment time of 3 years. [113] During the post-treatment years, liver-related hospitalization rates were almost 2.45 times higher in the non-SVR group compared with the SVR group. [113] Further, medicine and gastroenterology clinic visit rates were almost 1.39 time higher for non-treated patients.

One of the largest hepatitis C patient cohorts has been studied in the Chronic Hepatitis B and C Cohort Study (CHeCS) study that began following patients from four large health systems in 2006. Teshale et al. examined the effect of HCV treatment on hospitalization rates in this cohort through the year 2013 with a median follow-up

time of about 3 years. They followed 10,732 patients of which 1,505 had received HCV treatment. They found a 23% (p=0.02) reduction in hospitalization rates after treatment. [115] This study was conducted in the interferon era and so, consistent with other evidence in the literature, the discontinuation rates for interferon therapies were high due to side effects and the injection-based therapy. KPMAS' path of care coordination plays a key role in its high cure rate of 95%. [133] Close monitoring of and communication with patients helps to ensure patients are adhering to therapy and completing the DAA regimen as prescribed. This has long-term clinical and economic benefits - if patients complete therapy, the probability of cure is higher, reducing the rate of costly downstream healthcare resource utilization. [41]

These results highlight the need to understand the kinds of resources that DAA therapies could, or should, reduce and the length of time we need to assess this relationship. For example, reductions in the risk of resource-heavy conditions such as chronic kidney disease [187] or liver cancer may require greater follow-up in order to see a significant impact on emergency or inpatient resources. What specific disease processes do DAAs impact in a way that we would expect to see less necessity for those resources? A potential next step in this research could be to identify HCV-specific resource use as opposed to general visits and examine the impact of treatment on that utilization. Taking the aggregate approach, as we did in this study, however, can provide a broad sense of the impact of this utilization on the health system budget. Further, it is difficult to determine what resource use is specifically HCV-related when there are many extra-hepatic manifestations that can result from chronic HCV – metabolic and cardiovascular conditions are particularly difficult to separate out.

Evidence on adverse effects or positive spillover effects of DAA therapy on other medical conditions may provide some insight into whether or not we should have expected to find a significant effect. This is especially true in the short-term – clinical endpoints, such as glycemic control, may be detectable in six to twelve months after successful treatment but detecting a more aggregate impact on resource use, such as hospital admissions, may only be found in the long-term. This literature is just beginning to grow as more follow-up time accrues after DAA utilization – all-oral DAA therapies have only been widely available since 2014 and treatment uptake has been slow in some patient populations. [55] As utilization of DAAs continues to grow and become a part of routine HCV care, we will be able to better estimate the long-term impact of treatment on overall healthcare resource use.

To our knowledge, our study is the first to explore this research question in the second-generation DAA era. There remains much to be understood about the effects of DAA treatment. Although the first drug in this class, Sovaldi, was approved in November of 2014, we continue to see manufacturers develop and receive approval for new therapies for different subpopulations with varying duration of treatment. New studies focusing on different subpopulations of patients with Hepatitis C continue to provide more insight into the value of these drugs in patients with varying degrees of healthcare issues.

Conclusion:

One should not take the results of our study at face value and assume that downstream resource use does not significantly offset the cost of DAA therapy. The effects of DAAs on the long-term, most expensive clinical manifestations of HCV are uncertain. The bulk of the savings lie in the prevention of conditions such as end-stage liver disease and liver cancer since the disease is often asymptomatic in its earliest stages.

It is important to recognize that there is a significant gap in the literature exploring the effect of the new second-generation DAAs on healthcare resource utilization. The first of these therapies was developed and approved in November of 2013. This body of evidence will continue to grow as new DAAs make their way onto the market – Abbvie's pan-genotypic Mavyret received approval on August 3, 2017 from the FDA. This new DAA is the first treatment for chronic HCV with an eight-week therapy regimen. The shorter treatment duration is not only better for patients with regards to adherence and completion of therapy, but the list price is nearly 70% lower than that of Gilead's market leader Harvoni ($94,500 vs. $26,400). The effects of this new market entrant on clinical and economic outcomes will take many years to see given the number of drugs on the market, the diffusion time into routine practice and payers strategies to provide coverage for these prescription drugs.

As seen in our data, the majority of patients were treated with the second breakthrough drug Harvoni (sofosbuvir/ledipasvir), which received its FDA approval in November of 2014. In the context of the progression, or slowing of progression, of liver disease, it may take a few more years to generate enough real-world follow-up data to see the downstream utilization offsets. This study, although limited by follow-up time, was a first step to filling this gap in evidence.

Tables & Figures:

Figure 1: Conceptual Framework (Lipton & Bird) of Possible Factors Impacting Resource Use

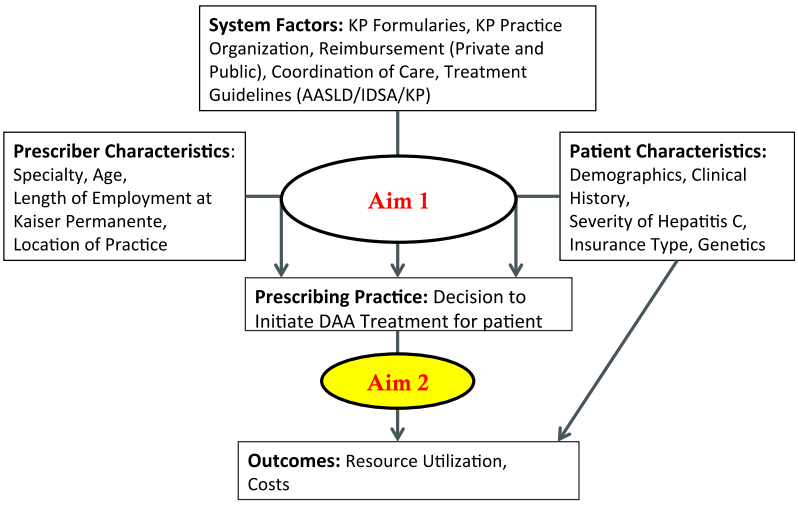


Table 1: Laboratory and Diagnostic Criteria for Identification of Chronic Hepatitis C Patients in KPMAS Hepatitis C Registry

Criterion 1: Positive HCV RNA results (either as "positive" if HCV RNA qualitative or level above lower limit of quantification if HCV RNA quantitative)
Criterion 1a: HCV genotype with published result NOT negative (which implies quantifiable HCV RNA in sample
Criterion 2: Two or more prescription refills of anti-HCV drugs within 365 days (It could be a patient who had two (2) or more prescriptions of the same anti-HCV drug dispensed within 365 days of each other, or one (1) prescription of two different anti-HCV drugs dispensed within 365 days of each other. Ribavirin will count if it has two or more prescriptions dispensed within 365 days but one prescription of ribavirin and one of another would not be okay because it acts as a booster for the other anti-HCV drug that is prescribed along with it.
Criterion 3: Positive Hepatitis C antibody and 2 or more HCV negative RNS tests after the first positive Hepatitis C antibody test.
Criterion 4a: A patient with a positive HCV antibody test PLUS 2 or more outpatient HCV coded visits by GI (Gastroenterology, GAS) or ID (Infectious Diseases) providers (Using earliest result date of AB lab test account for the patient)
Criterion 4b: Positive HCV antibody test PLUS 2 or more outpatient HCV coded visits by provider NOT GI or ID (Should be two or more visits to non-GI or non-ID provider, this also counts only one GI/ID and one or more non-GI/ID provider. Using earliest result date of AB lab test account for the patient).
Criterion 5: Positive HCV antibody test PLUS only 1 outpatient HCV coded visit by any provider (Using earliest result date of AB lab test account for the patient).

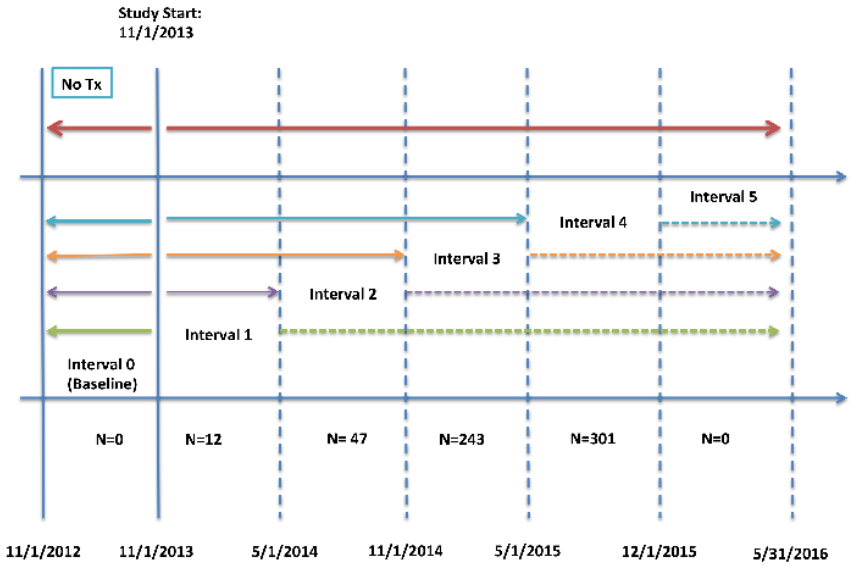
Table 2: Sample Size Requirements to Detect Effect Sizes of Varying Magnitude

Effect Size	N per group	N~=(4/effect size)^2	alpha	beta
0.1	1571	1600	0.05	0.8
0.2	394	400	0.05	0.8
0.3	176	178	0.05	0.8
0.4	99	100	0.05	0.8
0.5	64	64	0.05	0.8
0.6	45	44	0.05	0.8
0.7	34	33	0.05	0.8
0.8	26	25	0.05	0.8
0.9	21	20	0.05	0.8
1	17	16	0.05	0.8

Table 3: Distribution of Encounters by Type and Treatment Status (Frequency and Percent)

	All Patients		By Treatment Status	
Encounter Type	**Frequency**	**Percent**	**Untreated**	**Treated**
Ambulatory	90886	93.22	68160 (93.2%	22726 (93.3%)
Emergency Department	3343	3.49	2511 (3.4%)	832 (3.4%)
Inpatient	3209	3.29	2431 (3.3%)	778 (3.1%)
	97438	100	73102	24336

Figure 4: Study Period for Assessment of Panel Data Outcomes

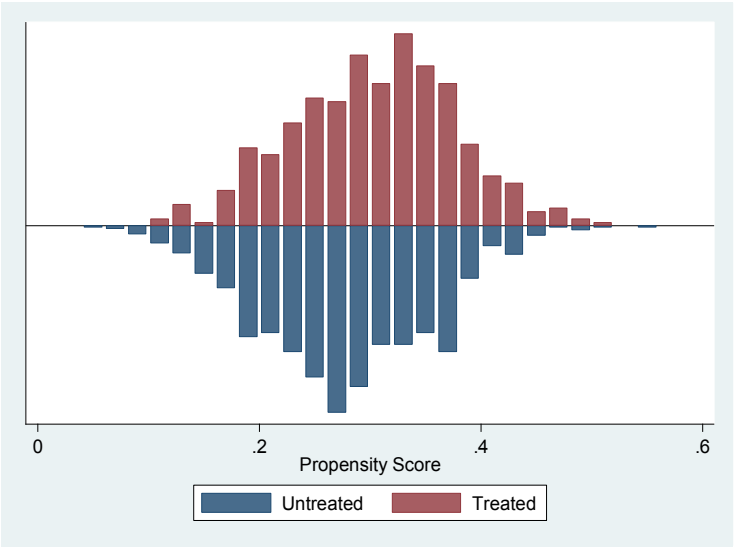


Notes: 1) No Tx, and the red arrow, represents how we followed patients who were never treated over the course of our study – their resource use measurements take place in the same way as for treated in each of the six intervals except without a break in measurements for treatment. 2) N=0 for interval 5 since we only included patients who had completed treatment by 12/1/2015 to ensure that patients had at least 6 months of 'post-treatment' time. N=0 for Interval 0 because this is in the baseline period before study start. 3) The solid lines represent the 'pre-treatment' period and the dotted lines represent the 'post-treatment' period. 4) The baseline period, or Interval 0, is between 11/1/2012 – 11/1/2013 – represented by left-facing arrows.

Table 4: Comparison of the Distribution of Patient Characteristics Before and After Propensity Score Matching

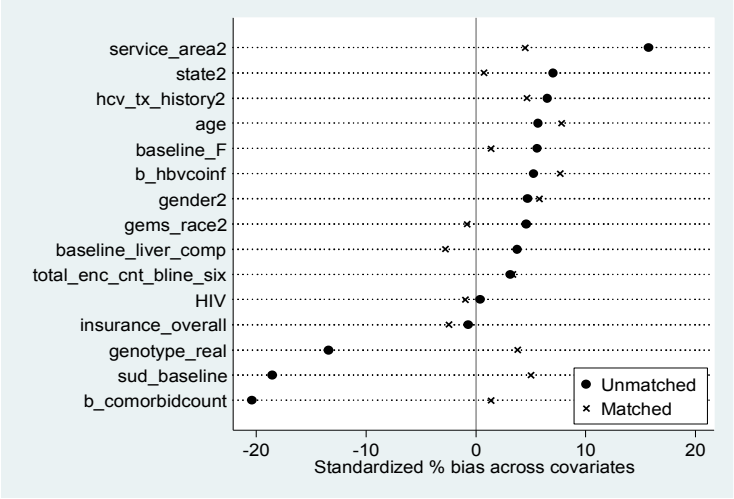
Unmatched (N=2533)				Matched (N=1347)			
Covariates	**Treated**	**Untreated**	**P-Values**	**Covariates**	**Treated**	**Untreated**	**P-Values**
Gender				**Gender**			
Male	385	1214		Male	291	593	
Female	218	716	0.674	Female	158	305	0.466
Age Category				**Age Category**			
20-40	13	87		20-40	11	27	
41-60	259	833		41-60	184	365	
61-80	327	964		61-80	251	500	
81-100	4	46	0.002	81-100	3	6	0.065
Patient State of Residence				**Patient State of Residence**			
DC	101	367		DC	78	156	
MD	340	1077		MD	249	498	
VA	160	470	0.338	VA	122	244	0.566
Race				**Race**			
API	23	79		API	19	38	
Black	1130	352		Black	274	548	
Hispanic	11	43		Hispanic	7	14	
Multi	-	-		Multi	-		
White	194	606	0.912	White	149	298	0.556
Insurance Type				**Insurance Type**			
Commercial	368	1235		Commercial	269	529	
Medicare	224	645		Medicare	173	345	
Medicaid	11	29		Medicaid	7	13	
Other	0	18		Other	0	8	
Duals	0	3	0.053	Duals	0	3	0.235
HCV Tx History				**HCV Tx History**			
Experienced	91	298		Experienced	70	135	
Naïve	512	1632	0.836	Naïve	379	763	0.239
Comorbidity Count				**Comorbidity Count**			
0	191	524		0	146	292	
1	220	705		1	161	322	
2	143	461		2	108	216	
3	42	184		3	27	54	
4	6	47		4	6	12	
5	1	8		5	1	2	
6	0	1	0.054	6	-		0.065
Baseline Liver Complications				**Baseline Liver Complications**			
0	524	1720		0	389	772	
1+	79	210	0.134	1+	60	126	0.489
Service Area				**Service Area**			
BALT	84	360		BALT	62	124	
DCSM	352	1094		DCSM	261	521	
NOVA	166	470		NOVA	125	250	
Network	1	6	0.041	Network	1	3	0.066
Baseline F				**Baseline F**			
1	136	462		1	129	259	
2	202	637		2	191	381	
3	137	403	0.584	3	129	258	0.64
Baseline Liver Complications				**Baseline Liver Complications**			
0	524	1720		0	389	772	
1+	79	210	0.134	1+	60	126	0.489
Baseline HBV Co-infection				**Baseline HBV Co-infection**			
No HBV Co-infection	594	1900		No HBV Co-infection	441	880	
HBV co-infection	9	30	0.914	HBV co-infection	8	18	0.26
Genotype				**Genotype**			
1	542	1316		1	409	818	
2	25	109		2	17	34	
3	15	63		3	11	22	
4	12	20		4	10	20	
5	0	2		5	-		
6	2	19	0.007	6	2	4	0.056
Baseline HIV				**Baseline HIV**			
HIV Positive	33	113		HIV Positive	27	54	
HIV Negative	570	1817	0.725	HIV Negative	422	844	0.93

Figure 5: Distribution of Propensity Scores for Treated and Untreated Patients



Notes: The figure demonstrates there is overlap of the propensity scores in both the treated and untreated groups.

Figure 6: Standardized Bias Plot for Covariates in Propensity Score Model



Notes: The x-axis shows direction and magnitude of standardized bias across the covariates included in the propensity score model. The dark circle shows this for the unmatched sample and the 'x' shows this for the matched sample. The further from 0, the greater the bias remains in the sample.

Table 5: Comparison of Bias in Unmatched vs. Matched Samples

Variable	Unmatched vs. Matched	Mean Treated	Mean Control	%bias	% reduction in bias	t-test	p>t
Age	U	60.826	60.329	5.7		0.98	0.328
	M	60.695	60.012	7.8	-37.4	1.1	0.27
Gender	U	1.6481	1.6254	4.7		0.84	0.4
	M	1.642	1.6143	5.8	-22.3	0.84	0.399
Service Area	U	2.1448	2.0433	15.7		2.8	0.005
	M	2.1178	2.0889	4.5	71.6	0.67	0.502
Race	U	2.9688	2.9028	4.6		0.83	0.409
	M	2.97	2.9815	-0.8	82.5	-0.12	0.906
Insurance	U	1.4165	1.4205	-0.7		-0.13	0.901
	M	1.4088	1.4226	-2.5	-245.2	-0.37	0.714
Baseline F	U	2	1.9576	5.6		1	0.315
	M	1.9931	1.9827	1.4	75.5	0.2	0.841
Baselne Comorbid Count	U	1.0846	1.2924	-20.4		-3.6	0
	M	1.1201	1.1062	1.4	93.3	0.21	0.834
Baseline Liver Complications	U	0.13363	0.12102	3.8		0.68	0.494
	M	0.12933	0.13857	-2.8	26.7	-0.4	0.69
Baseline SUD	U	0.26949	0.35512	-18.5		-3.27	0.001
	M	0.27945	0.25635	5	73	0.77	0.443
State	U	2.098	2.0521	7		1.27	0.205
	M	2.0716	2.067	0.7	89.9	0.1	0.917
Tx History	U	1.8441	1.8198	6.5		1.15	0.25
	M	1.843	1.8256	4.6	28.7	0.68	0.494
Genotype	U	1.1759	1.2739	-13.4		-2.3	0.021
	M	1.1824	1.1547	3.8	71.7	0.69	0.488
HBV Baseline	U	0.01782	0.01148	5.3		0.99	0.322
	M	0.01617	0.00693	7.7	-45.9	1.27	0.204
HIV Baseline	U	0.06013	0.05919	0.4		0.07	0.943
	M	0.06236	0.06467	-1	-144	-0.14	0.889
Baseline Use	U	12.223	11.805	3.1		0.56	0.576
	M	12.293	11.848	3.3	-6.6	0.49	0.626

Sample	Ps R2	LR chi2	p>chi2	MeanBias	MedBias	B	R
Unmatched	0.025	48.03	0	7.7	5.6	39.1*	0.86
Matched	0.006	7.09	0.955	3.5	3.3	18	1.01

Notes: The '% bias' column provides an estimate of the magnitude and direction of the bias. Positive values bias remaining in the direction of the matched treated group; negative values show bias in the direction of the matched control group. The '% reduction in bias' column shows the percent reduction in bias from the unmatched to the matched sample. A positive % reduction indicates the percentage bias in the sample decreased from unmatched to matched; a negative % reduction indicates the % bias in the sample increased from the unmatched to the matched sample. The t-test, and its associated p-value, tests the null hypothesis that the distribution in a particular covariate does not differ across treatment groups (treated vs. control). The overall median and mean bias successfully decreased to below 5%. Explanation of specific covariates can be found in the section "Assessment of Propensity Score Matching."

Table 6: Number of Patients Treated in Each Interval

Interval 0	Interval 1	Interval 2	Interval 3	Interval 4	Interval 5
Pre 11/1/2013	11/1/2013 - 5/1/2014	5/1/2014 - 11/1/2014	11/1/2014 - 5/1/2015	5/1/2015 - 12/1/2015	12/1/2015 - 5/31/2016
0	12	43	222	172	0
0%	2.67%	9.57%	49.40%	38.30%	0%

Notes: Interval 0 is considered the baseline period or prior to study start, November 1, 2013, and subsequent follow-up period. Given the minimum six-month follow-up criteria we imposed on patients to be eligible for our analytic sample, no patients in our sample were treated in interval 5. These are patients included in the matched sample.

Table 7: Resource Utilization Per Interval by Encounter Type Over Study Period

Type of Encounter	Treatment Group	Interval 0	Interval 1	Interval 2	Interval 3	Interval 4	Interval 5
N	Treated	0	12	55	277	449	449
	Untreated	1347	1335	1292	1070	898	898
All	Treated	N/A	Mean: 2.33; Median: 2	Mean: 5; Median: 3	Mean: 6.27; Median: 3	Mean: 6.48; Median: 3	Mean: 5.65; Median: 3
	Untreated	Mean: 10.9; Median: 7	Mean: 5.23; Median: 3	Mean: 5.65; Median: 3	Mean: 5.44; Median: 3	Mean: 6.05; Median: 3	Mean: 4.73; Median: 3
AV	Treated	N/A	Mean: 2.33; Median: 2	Mean: 4.90; Median: 3	Mean: 5.95; Median: 3	Mean: 6.06; Median: 3	Mean: 5.32; Median: 3
	Untreated	Mean: 10.24; Median: 6	Mean: 4.80; Median: 3	Mean: 5.23; Median: 3	Mean: 4.99; Median: 3	Mean: 5.6; Median: 3	Mean: 4.56; Median: 3
ED	Treated	N/A	Mean: 0; Median: 0	Mean: 0.046; Median: 0	Mean: 0.216; Median: 0	Mean: 0.269; Median: 0	Mean: 0.109; Median: 0
	Untreated	Mean: 0.345; Median: 0	Mean: 0.201; Median: 0	Mean: 0.212; Median: 0	Mean: 0.231; Median: 0	Mean: 0.225; Median: 0	Mean: 0.099; Median: 0
IP	Treated	N/A	Mean: 0; Median: 0	Mean: 0.046; Median: 0	Mean: 0.108; Median: 0	Mean: 0.177; Mean: 0	Mean: 0.219; Median: 0
	Untreated	Mean: 0.315; Median: 0	Mean: 0.229; Median: 0	Mean: 0.210; Median: 0	Mean: 0.213; Median: 0	Mean: 0.214; Median: 0	Mean: .066; Median: 0

Notes: The row titled "N" shows the number of patients in each of the treatment group over time. As in Table 6, all patients in our analytic sample begin untreated as of 11/1/2013. With each subsequent interval, patients that are treated are moved to the "Treated" status. As operationalized in the panel data setup, once a patient is treated in a given interval, he or she remains treated for the remainder of the study. There is no difference between interval 4 and interval 5 because no additional patients are treated in interval 5. The 'All' encounters here are the "adjusted" total encounters – adjusted according to ratio of average costs of type of encounter.

Table 8: Treatment and Treatment Interval Effects – Longitudinal Random Intercept Models (N=1347)

Coefficients	IRR	Std. Err	P>|z|	95%	CI
All					
Tx	0.9099013	0.0762426	0.059	0.760465804	1.0593368
Tx in Interval 1	0.9211221	0.1764607	0.668	0.6327779	1.340859
Tx in Interval 2	1.188336	0.116404	0.078	0.9807523	1.439856
Tx in Interval 3	1.075028	0.052828	0.141	0.9763167	1.183719
Tx in Interval 4	1.019662	0.0440521	0.652	0.9368763	1.109764
AV					
Tx	0.8871346	0.074879	0.067	0.74036286	1.03388854
Tx in Interval 1	0.8757485	0.1620533	0.473	0.6093523	1.258608
Tx in Interval 2	1.168381	0.1102254	0.099	0.97114	1.405682
Tx in Interval 3	1.106127	0.0525714	0.034	1.007742	1.214116
Tx in Interval 4	1.040161	0.0434608	0.346	0.9583742	1.128928
ED					
Tx	0.7057071	0.1770849	0.145	0.358620696	1.0527935
Tx in Interval 1	0.9302715	0.5983359	0.911	0.2637122	3.281626
Tx in Interval 2	1.038187	0.3161231	0.902	0.5715958	1.885656
Tx in Interval 3	1.410084	0.177261	0.006	1.102151	1.804053
Tx in Interval 4	1.181858	0.1326543	0.137	0.9484719	1.472672
IP					
Tx	0.8110677	0.1098042	0.073	0.595851468	1.02628393
Tx in Interval 1	0.326391	0.3502622	0.297	0.0398366	2.6742
Tx in Interval 2	1.157292	0.407677	0.678	0.5802188	2.30831
Tx in Interval 3	1.188061	0.1885846	0.278	0.870412	1.621633
Tx in Interval 4	1.177214	0.1657985	0.247	0.8932486	1.551452

Table 9: Treatment and Treatment Interval Effects – Population Averaged Model (N=1347)

Coefficients	IRR	Std. Err	P>|z|	95%	CI
All					
Tx	0.957392	0.0436924	0.34	0.8754747	1.046974
Tx in Interval 1	0.4410095	0.0869546	0	0.2996506	0.6490539
Tx in Interval 2	0.9904567	0.0981012	0.923	0.8156935	1.202663
Tx in Interval 3	1.068982	0.0526052	0.175	0.9706939	1.177222
Tx in Interval 4	1.134926	0.0486354	0.003	1.043496	1.234368
AV					
Tx	0.9974163	0.0447176	0.954	0.9135118	1.089027
Tx in Interval 1	0.9983939	0.0022579	0.477	0.9939782	1.002829
Tx in Interval 2	0.5893382	0.1415241	0.028	0.3680921	0.943567
Tx in Interval 3	1.150594	0.1378454	0.242	0.9097977	1.455121
Tx in Interval 4	1.041663	0.0612404	0.487	0.9282913	1.168881
ED					
Tx	0.8224852	0.1141257	0.11	0.598798828	1.04617157
Tx in Interval 1	1.00421	0.0042955	0.326	0.9958257	1.012664
Tx in Interval 2	0.5510331	0.3462506	0.343	0.1608093	1.888183
Tx in Interval 3	0.6758105	0.1926109	0.169	0.3865683	1.181472
Tx in Interval 4	1.354756	0.1398826	0.003	1.106553	1.658633
IP					
Tx	0.794014	0.113864	0.076	0.57084056	1.01718744
Tx in Interval 1	0.1239835	0.134234	0.054	0.0148521	1.034998
Tx in Interval 2	0.4756907	0.1493086	0.018	0.2571294	0.8800303
Tx in Interval 3	1.200989	0.1248159	0.078	0.9796612	1.472321
Tx in Interval 4	1.279465	0.114403	0.006	1.073788	1.524538

Aim 3: Cost-Effectiveness of Triage Treatment Strategies in an Integrated Healthcare System

Introduction:

While studies have demonstrated unprecedented cure rates for the new direct-acting antivirals for the treatment of Hepatitis C (HCV), the high list prices set by manufacturers have motivated a quest for a measure of value of these drugs. Cost-effectiveness analyses use a cost per outcome metric to demonstrate the value of a treatment or medical practice. Although not formally part of the drug approval process in the United States, many have undertaken these studies for the multitude of available DAAs to demonstrate their clinical and economic value. [93] Systematic reviews of cost-effectiveness analyses comparing different DAA regimens demonstrate that the value of these therapies differs depending on the patient population examined. [105-107] The evidence, however, is overwhelmingly in favor of these therapies – they are cost-effective compared to standard willingness-to-pay thresholds. [105, 106] More studies in different real-world patient populations, healthcare settings and payer scenarios are also necessary.

An ideal therapy for chronic HCV is effective in different patient populations, convenient in terms of administration, safe, accessible and affordable to all patients and has a high barrier to resistance - accessibility and affordability are currently the most difficult characteristics to achieve in the United States. [2] Given the substantial economic burden associated with the use of these new direct-acting antiviral therapies as highlighted by the dilemmas all payers and providers face, it is important to assess or quantify the value of such treatment practices. If patients diagnosed with HCV have to wait for treatment until they have developed further complications despite the AASLD guidelines to the contrary, we must be able to demonstrate an argument for efficiency to the multiple stakeholders involved in this decision-making process. The objective of this study is to assess the value, or cost-effectiveness, of different levels of this triaging practice operationalized by treatment at increasing levels of disease severity from the perspective of an integrated healthcare system.

Problem Statement

The new DAA therapies offer a cure to an infectious disease that affects between 2.7 and 4.1 million patients in the United States. [13] However, their curative nature has created both policy and public health problems that researchers continue to address through health economics and health services research platforms. While the new

drugs are extremely expensive for payers, systems and ultimately patients, the issue is not simply one of affordability – the high prices have externalities. Specifically, providers and health systems may triage patients – patients with more advanced liver disease may be treated immediately, while HCV patients with lower fibrosis scores are recommended for monitoring or in some severe cases, coverage is denied by payers if patients don't meet certain illness criteria. While manufacturers state the value of their therapies will be realized in the long-term by preventing more severe manifestations of HCV, healthcare systems and payers, both private and public, must work within their budget constraints. They have to be able to provide care for diverse populations with a wide variety of healthcare needs.

Triaging patients, in the context of HCV, means treating those with the most advanced liver disease first and delaying therapy for patients with minimal liver fibrosis. CMS initially imposed harsh restrictions on reimbursement based on fibrosis stage, but have since loosened restrictions due to lawsuits. Triaging, sometimes referred to as warehousing, is not often seen in other disease contexts with highly expensive therapeutic regimens such as oncology or anti-retroviral therapy. This comparison sparks highlights what makes HCV a unique disease for which denying coverage for therapy has been an issue – many feel the stigma associated with its primary source of infection, injection drug use, could be a motivating force behind these practices. This analysis will provide some insight to policymakers, providers and health care systems on the most efficient treatment algorithm.

Study Design & Scope

Objective

In this study, we examined the cost-effectiveness of immediate treatment with DAA therapy for chronic HCV patients in comparison to delaying DAA treatment in an integrated health care system. This comparison was operationalized as four different treatment strategies: Treat All, Treat F1+, Treat F2+ and Treat F3-F4 (Figure 1). These are described in further detail below. We compared the resulting incremental cost-effectiveness ratios to the $150,000/QALY willingness-to-pay (WTP) threshold recommended for the United States health care setting. [188]

Audience

The primary audience for this study is the Kaiser Permanente (KP) Mid-Atlantic States integrated health care delivery system, which is comprised of the Kaiser Foundation Health Plan of the Mid-Atlantic States (KFHPMA) and the Mid-Atlantic Permanente Medical Group (MAPMG). KFHPA and MPAMG, like all of the eight KP regions across the U.S., have a shared responsibility to provide high value care to its members. [189] To achieve this goal, KFHPMA and MPAMG are aligned and accountable for a global budget that is negotiated annually for the provision of medical services. The medical group is responsible for the clinical care, quality improvement, resource management and the design and operation of the care delivery system. Given the "pre-paid" structure, the medical group is not reimbursed based on the level of services required by or used by a specific beneficiary. In addition, KFHPMA is a 501c3 non-profit and invests back into its members, their community and research to help achieve the joint KP mission "to provide affordable, high-quality health care services to improve the health of our members and the communities we serve."

Some key parameters derived from the data from the first analysis in this body of work. It is important to note that the resource costs included in this analysis do not reflect the payment mechanisms by which services are reimbursed or physicians are paid in the KPMAS integrated health care system. There are unique aspects of this type of health care system, which are not incorporated in this Markov model. While we discuss the implications of these factors in a later section, these limit applicability of the results to the KPMAS health care system. However, they do increase the generalizability of the results to other health care settings.

Secondary audiences include other health care payers – both private and public – to demonstrate the cost-effectiveness of providing coverage for these drugs without restrictive criteria, clinical or otherwise.

Type of Analysis

We performed a cost-effectiveness analysis using a Markov model. Using this approach, we performed a cohort analysis using a hypothetical cohort of patients infected with chronic HCV. The resulting incremental cost-effectiveness ratio (ICER) quantifies the cost per additional quality-adjusted life-year – when decision makers are faced with choices across different disease contexts, this 'price' facilitates comparisons across interventions.

We also performed sensitivity analyses to test the robustness of our results to the uncertainty in the data and underlying assumptions. These include deterministic, both one-way and two-way, sensitivity analyses, and probabilistic sensitivity analyses. [188] One-way sensitivity analyses are used to vary select parameters, one at a time, while two-way sensitivity analyses vary two key parameters simultaneously to determine their impact on the resulting ICER. It illustrates, to the decision maker, the most influential parameters on the optimal strategy choice.

We also performed probabilistic sensitivity analyses (PSA) in which multiple model simulations are run in which the model selects the value of a parameter from specific distribution. [190] PSA characterizes uncertainty in all of the parameters of interest simultaneously more realistically reflecting the uncertainty of any particular decision-making process. These results are illustrated using cost-effectiveness acceptability curves to demonstrate the probability of a certain intervention, or treatment strategy, being cost-effective at a certain WTP threshold.

Finally, we conducted a value of information (VOI) analysis. The results of this analysis quantify a potential increase in net monetary benefit from having "perfect" information on the uncertain parameters in the model. The EVPI, or expected value of perfect information, per person is how much we would need to invest in research to increase our confidence in the recommendation of the optimal strategy. It can provide a societal level estimate of a budget for future research.

Target Population

The target population for this study was patients infected with chronic Hepatitis C.

Description of Intervention & Comparator

All patients were treated with a DAA in our model. However, the timing of treatment over the course of the model horizon was dependent upon disease severity or F-score (Figure 1). In the data sample from KPMAS, majority of the patients were treated with ledipasvir/sofosbuvir.

Other Intervention Descriptors

We used the cure rate from the KPMAS data sample. This measure of effectiveness better approximates real-world outcomes over the currently, most commonly, used clinical trial efficacy rates. We found that amongst

those treated, ~95% of patients achieved cure, as per the lab results available from KPMAS electronic health record. As per KPMAS' care pathway, patients not immediately treated are monitored closely by primary care physicians. [133] In addition to care navigators, clinical pharmacists are also an integral component of this process. They review the prescribed medications and order any laboratory testing in this care pathway. There is an annual monitoring cost for patients who are not treated immediately – this includes vibration controlled transient elastography, CBC panels, hepatic function panels and alpha-fetoprotein tests – until they are ultimately referred to a specialist. Adherence-monitoring costs are included in the model cycle immediately following treatment.

Scope of the Analysis

Although chronic HCV is an infectious disease, we focused on the comparison and impact of the multiple treatment approaches in a closed cohort of HCV patients.

Time Horizon

We conducted the primary cost-effectiveness analysis over a 30-year time horizon. Given the chronic nature of HCV and the many years necessary for disease progression, we focused on the long-term assessment of the value of these treatment decisions to adequately capture differences in outcomes. Each cycle in the model was one year in length – all parameters were annual unless otherwise specified. We also conduct an analysis from the health care sector perspective using a 15-year time horizon to capture enrollment duration in private health plans.

Discounting

Although our model spans a time horizon of 30 years, decision makers assess the value of these different treatment strategies derived today rather than some time in the future. [191] By discounting, we determined the present value of any utility, or cost savings, gained in the future to facilitate a fair comparison across treatment strategies. We used a 3% discount rate for both costs and QALYs for the base case analysis as is recommended. [191]

Analytic Perspective

As per the recommendations from the Second Panel on Cost-Effectiveness in Health and Medicine [188], we used two perspectives: the U.S. healthcare sector and U.S. societal perspectives.

We highlight the results from the healthcare sector perspective given that it is linked to resource implications considered by decision makers. The intended audience from this perspective was Kaiser Permanente Mid-Atlantic States Integrated health care system. However, the KP payment model differs from other traditional third-party payers. As described in more detail above, the medical groups negotiate an annual global budget with the health plan for the services they will provide – physicians are not paid per service provided.

All costs were derived from the literature since we did not have access to any payment information from the KP system. From the healthcare sector perspective, we included formal healthcare, or medical, costs. Current costs included resources such as DAA treatment costs and HCV state-specific healthcare costs. Future costs included resources such as annual monitoring costs for liver cancer screening. We did not explicitly differentiate the out-of-pocket costs faced by patients.

We also conducted the analysis from the societal perspective. This included caregiver costs for patients who have developed the most severe manifestations of chronic HCV and income losses for these same patients who are forced to leave their jobs due to the disease or treatment for its symptoms. We used a human capital approach, using an average measurement of income, to quantify loss of productivity. The indirect costs included in the societal perspective demonstrate that the effects of the disease, as well as treatment, are not just physiological or medical.

In the societal perspective analysis above, we assumed indirect costs would only accrue to patients with the most severe disease (stage F3 or above). We conducted a separate subgroup analysis using an "expanded" societal perspective in which we allowed patients at all stages of the disease to experience some magnitude of indirect costs. These costs were linked to the health state utilities experienced by patients in each of those health states. This relationship is discussed in more detail in a later section.

Analysis Plan

Conceptual Model

We first reviewed the cost-effectiveness literature in the chronic HCV space to understand how treatment policies for HCV have been modeled before. [96, 99, 101, 109, 110, 192-195] Further, in consultation with various experts with different backgrounds – infectious disease epidemiology, health economics and hepatology – we developed a conceptual model that demonstrates the pathway patients follow as a result of the initial treatment decision. Figure 1 provides a schematic we developed that shows the various possible pathways a patient can take once a treatment decision has been made. We show the initial decision node (Figure 1) in the model that simulates patients through each of the four treatment policies: Treat All, Treat F3 – F4 +, Treat F2+ or Treat F1+. The Markov structures for the all policies look similar except based on the selected policy only patients in certain disease stages can be treated.

Patients begin in one of the five fibrosis stages: F0 (no fibrosis), F1 (portal fibrosis without septa), F2 (portal fibrosis with rare septa), F3 (Numerous septa), or F4 (Compensated cirrhosis). Patients in fibrosis stages F0-F3 can progress to the next stage of fibrosis or can remain in the initial state in each cycle of the model. Patients with compensated cirrhosis, or in the F4 stage, are at risk of developing either decompensated cirrhosis or hepatocellular carcinoma. Patients are then at risk of HCV-related death or may need a liver transplant.

If patients are treated and cured, patients from any stage can either remain in the state they were prior to treatment or still experience an extremely small probability of progressing to the next stage of the disease. Patients with decompensated cirrhosis can also continue to progress to liver cancer or need a liver transplant even after cure – cirrhotic or more severely ill patients still have a small likelihood of developing liver cancer and that possibility is represented in the model. If patients fail treatment, they progress naturally through HCV. Finally, there is always an underlying risk of mortality for all patients and this is operationalized by the terminal state of death.

Data Collection Plan

Majority of the model parameters for this study were derived from the current cost-effectiveness and epidemiologic literature in the HCV space. However, two of the key treatment parameters were estimated from a study sample of chronic Hepatitis C patients from the Kaiser Permanente Mid-Atlantic States EHR and HCV registry. We estimated probability of cure and the initial distribution of patients across fibrosis scores. Stage specific

costs, DAA costs and health state utilities were all derived from the literature. It is important to note that these costs are not necessarily reflective of the payment model and overall system structure of the KPMAS system.

Methods & Data

Model Overview

We constructed a decision-analytic model of chronic HCV to examine the costs and quality of life outcomes of treatment initiated at different fibrosis stages over the course of the HCV infection. We model these staged treatment policies as the following options: treat all patients, or universal treatment (F0-F4), treat patients with only severe fibrosis (F3-F4), treat patients with moderate to severe fibrosis (F2 or above), and treat patients with fibrosis scores of F1 or above. These staged treatment policies operationalize how patients are triaged in different settings. [63, 70, 133] Specifically, providers may have to demonstrate that a patient has reached an advanced fibrosis stage (F3-F4) in order for the insurer to cover therapy – previously the case in many state Medicaid programs. In other settings, the payer has expanded access to patients with even the mildest disease (F0-F4) – currently the case in the VA. Currently, the workflow at KPMAS is to refer patients with a fibrosis score of F2 or above to see a specialist who can directly discuss and prescribe DAAs to the patient (as required by Maryland and Virginia CMS rules), while those with stage 0 or 1 fibrosis are monitored in primary care. [133] A patient can request and receive a referral at any time, regardless of fibrosis stage.

The disease stages reflect progression through the 5 METAVIR (Meta-analysis of Histological Data in Viral Hepatitis) liver fibrosis stages (F0, no fibrosis; F1, portal fibrosis without septa; F2, portal fibrosis with rate septa; F3, numerous septa without cirrhosis; and F4, cirrhosis) to advanced liver disease. We simulated a closed cohort of treatment-naïve HCV patients until death, tracking costs and quality-adjusted life-years discounted to present value. We validated the model by comparing predictions with results of prior models.

Treatment Characteristics

Currently, there are multiple therapies for HCV genotype 1 infection approved by the US Food and Drug Administration. The goal of treatment is an undetectable serum level of HCV RNA 12 weeks after completion of therapy, or sustained virologic response. The likelihood of a sustained virologic response was, as discussed above,

estimated from observational data from the HCV registry at KPMAS. During our study period, between November 1, 2013 and May 31, 2016, the most commonly used DAA was ledipasvir/sofosbuvir (Harvoni) and therapy was 12 weeks in duration. We calculated an overall cure rate for all treated patients in the sample.

We used therapy regimen start and stop dates, lab results, and electronic health record data to determine how many of the treated patients achieved SVR after completion of therapy. Of the 776 patients who were treated in our study sample, 738 (95%) achieved a cure. The rate of SVR was assumed to be the same for all patients.

Natural History of Chronic HCV

Chronic HCV progression through increasingly severe liver fibrosis is classified with fibrosis scores F0 to F4. We used these scores and the more severe clinical manifestations to define Markov model disease states. These included decompensated cirrhosis, hepatocellular carcinoma and liver transplant. Transition probabilities between states are based on our review of the published literature. The model begins with a cohort in which HCV-infected patients are distributed across the 5 stages of fibrosis. Patients can continue to progress through the stages of disease after treatment success and failure – the rates of progression vary based on whether or not the patient achieved cure.

Using the F scores at the beginning of our observational period, we were able to determine the probability of initially being in any given stage of disease severity (F0-F4). We had 2,228 patients with a record of an F-score and the distribution is as follows: F0: 105 (.05), F1: 572 (.25), F2: 933 (0.41), F3: 533 (0.25), and F4: 85 (.04). We varied this distribution in the probabilistic sensitivity analysis to account for variability across settings.

Treatment Strategies

We aimed to assess the cost-effectiveness of the timing of treatment in the context of disease severity. In the 'Treat All' strategy, patients from any initial fibrosis stage could be treated. They can achieve cure, experience treatment failure or can progress through to more severe stages of the disease. In the 'Treat F3-F4' strategy, patients with fibrosis scores of F3-F4, have the opportunity to be treated and cured, fail treatment and subsequently progress in disease. In the 'Treat F2+' strategy, patients with fibrosis scores of F2 or above have the opportunity to be treated and cured, fail treatment and subsequently progress in disease. These patients can remain in their initial disease stage or can progress to more severe fibrosis stages. Finally, in the 'Treat F1+' strategy, patients with fibrosis scores of F1

or above can be treated and cured, fail treatment and subsequently progress in disease. Patients with a fibrosis score lower than indicated in the treatment strategy cannot be treated in that strategy. We did not use the 'no treatment' option as a comparator as it is neither an ethical treatment strategy given that the new DAAs are the standard of care nor a realistic option given the multitude of available treatment options available for chronic HCV patients.

KPMAS' most recent care pathway implements the 'Treat F2+' strategy. However, in a previous analysis of a sample of HCV patient data from KPMAS' data, we found no differences in the distribution of fibrosis scores by treatment status. This shows that while this 'cut-off' score of F2 is formalized in the care pathway, there are exceptions to this rule. Physicians can make case-by-case decisions about treatment given other complicating comorbidities, any abnormal test results or a patient's request for immediate referral for treatment. [133]

Mortality

We assumed that mortality for patients with stages F0 to F2 was assumed to be equal to the mortality rate of the general population. [196] Mortality for patients with stages F3 and F4 and no cure is 2.37 times the age-specific background rates from US life tables and based on evidence from a prospective cohort study. [196, 197] Individuals with decompensated cirrhosis and hepatocellular carcinoma have higher mortality rates than those without cirrhosis. [198] HCV patients who receive a liver transplant have a risk of death from transplant-related complications. [40]

Treatment Costs

The available DAAs on the market vary substantially in the initial list price the manufacturer sets – Gilead's Harvoni (sofosbuvir/ledipasvir) is set at an initial list price of $94,500 for a 12-week course of treatment.

Payers, both public and private, negotiate discounts off this price. However, we did not have access to information about what Kaiser Permanente's prescription drug plan pays for any of the DAAs. We used the list price of the most recently approved drug, Mavyret, as the price of the drug in the base case analysis. By doing so, we can provide some evidence of the most cost-effective treatment strategy if, and when, the health system places this drug on their formulary to reflect the treatment options. We varied these prices substantially, from the potentially cheapest generic version of the drug ($4) to the highest list price possible ($94,500), in sensitivity analyses to demonstrate the impact of drug cost on the value of any particular treatment strategy.

We operationalized treatment cost as a one-time prescription drug cost in the transition between an initial model stage and cure or failure. As part of KPMAS' HCV care pathway, once patients are treated, there is a cost of adherence monitoring, a follow-up HCV RNA assessment and a cost of testing for a sustained virologic response. Each of these costs is included with the one time drug cost in the model. After treatment, patients at KPMAS are screened annually for liver cancer if the patient was cirrhotic at the time of treatment – this cost is added to the drug cost. For all costs, indirect and direct, we adjust costs for inflation to 2016 US dollars using the Medical Care Consumer Price Index. [199]

Direct Costs

We reviewed the current literature for studies estimating direct health care costs associated with chronic HCV by stage of disease. Some studies generated estimates based on analyses of nationally representative datasets [40] and others conducted on patients in an integrated health care system. [200] We reviewed multiple studies [20, 68, 201, 202] for annual cost values and chose estimates based on studies from managed care systems to more closely approximate those of our commercial insurer audience. [20, 68] Specifically, we used maximum and minimum values across these studies in one-way sensitivity analyses. We used a gamma distribution on the annual health state costs as part of a probabilistic sensitivity analysis described in more detail below.

In our model, when patients were not treated, they either remained in the same stage of disease or they had a chance to progress to advanced stages of disease. Without treatment, this annual healthcare cost remained the same over the course of each cycle in the model as the disease naturally progresses. However, when a patient was successfully treated, that annual health state cost is reduced to some fraction of the annual treatment cost.

As discussed above, we modeled patient follow-up and annual monitoring to reflect the current care pathway in place at KPMAS. [133] The specific costs for each of these particular tests are based on values in the literature used in previous economic evaluations. [101, 203-205] The annual monitoring costs for untreated patients were accounted for in the annual health state costs for those not treated in the model.

Although both care navigators and clinical pharmacists are involved in this care pathway, we did not assign a value, or cost, to their time in this process. Instead, we assigned a cost to the tests or monitoring ordered for patients to provide dollar estimates of resources used – potentially biasing costs downward.

Indirect Costs

We included two types of indirect costs in the societal perspective: caregiver costs and potential lost income for patients with advanced liver disease who may require informal caregivers and are out of work for an extended period of time. We used a human capital approach to assign a dollar value to loss of productivity.

Given the United States societal perspective we are taking in the analysis, we used the national median annual household income as the basis for calculating potential loss of income, or lost productivity. Specifically, according to Kaiser Family Foundation State Health Facts, the 2016 national median annual household income was $59,039.[206] We tied the loss of income to the decrement in health state utility (1 – the utility in given state) associated with a particular disease state during which patients are likely to be out of work. The assumptions surrounding the operationalization of this indirect cost is discussed further in the section on modeling assumptions. We varied this in both deterministic and probabilistic sensitivity analyses to capture the variation across the three states KPMAS serves: District of Columbia ($70,982), Maryland ($73,760) and Virginia ($66,451).

In consultation with a hepatologist, we determined that patients with decompensated cirrhosis or more advanced disease would certainly require constant informal care in additional to formal medical care in a hospital setting. During the earliest stages of the disease, minimal to no fibrosis (F0-F2), HCV is usually asymptomatic and informal care is usually not necessary. Once patients develop cirrhosis, during stage F4, the magnitude of additional informal care they may require varies depending on the manifestations they have. Some patients, with particularly complicated disease, may have some kidney involvement – renal disease, and dialysis, can lead to further complications. Patients may also experience debilitating fatigue or diabetic complications that could generate other indirect costs.

Rakoski et al. formally quantified the number of informal caregiver hours and subsequent annual costs for older adults with cirrhosis, compared to those who had not developed cirrhosis, using a cohort from the nationally representative Health and Retirement Study. They found that patients with cirrhosis received over two times the number of informal caregiver hours per week resulting in an annual cost of about $4,700 per person (2012 US$).[207] Using the medial national wage for a home health aide and the mean number of informal hours per week received, researchers estimated an annual cost of informal care. We employed the same calculation using updated wage information for home health aides in 2016 – the median hourly wage for home health aides in 2016, according to the

Bureau of Labor Statistics, was $10.87. [208] Cirrhotic patients require on average about 9.14 hours of informal care a week, multiplied by 52 weeks in a year, yields $5,166.29 annual informal costs. Although Rakoski et al. studied this in older adults, we are comfortable with these estimates as progression to advanced stages takes years – about 90% of the patients in our KPMAS study sample were between the ages of 41-80 at study start.

We included the annual cost of informal care in pre-treatment stages of F4, decompensated cirrhosis (DCC), hepatocellular carcinoma (HCC) and liver transplant (LT). We also included an annual cost of informal care in cured stages of F4, DCC, HCC and LT – the cost was reduced by an amount proportional to the increase in health state utility achieved once these patients reached the SVR state. For example, patients in stage F4 prior to treatment, have a utility of 0.76 and after cure, this increases to 0.83. We reduce the annual informal care cost by the difference between these utilities ($5,166.29 – ($5166.29 * .07)). We varied this cost in sensitivity analyses.

Health State Utilities

Health state utilities were also derived from the literature – we know that there are many measurement techniques (rating scale, time trade-off or standard gamble) by which utilities are determined and can result in different valuations of the same state. [209-211] We reference studies that estimated health state utilities from the SF-36. [201, 212] We varied these in sensitivity analyses to account for variation in utilities elicited from different metrics.

The health state utilities were then used in the model to calculate quality-adjusted life years (QALYs) - the measure of effectiveness in our analysis. The QALY, is a generic measure of disease burden that takes into account both the quality and quantity of life. They allows for comparisons across interventions.

Modeling Assumptions

Healthcare costs included in this study were specific to chronic HCV and did not include potential healthcare costs incurred due to any of the multiple extra-hepatic manifestations (EHMs) that could develop. By excluding these potential costs incurred by HCV patients who develop these EHMs, there may be even more cost offsets into the future if patients are treated earlier with DAAs.

We assumed once a patient has achieved cure they remain in that state or can, with minimal likelihood, progress to the next advanced disease stage. The cost of the SVR state after being cured from stage F0 is a fraction

of the health state cost associated with being in the F0 state. We apply the same adjustment to each unique SVR state. This reflects the reality of the disease in which, upon cure, all disease symptoms and signs do not subside immediately. After consultation with a hepatologist about the reduction in health state costs after cure, we assumed that this reduction was greatest for those in the earliest stages (F0-F2) – annual costs after cure was 25% of the initial cost. The reduction in annual cost for stages F3-F4 after cure was 50% of the pre-treatment costs. Finally, patients cured after treatment of the infection in the most severe stages – decompensated cirrhosis (DCC), liver cancer (HCC) and liver transplant (LT)– likely experience the least of these reductions in costs and so we assume only a 25% drop in annual state costs.

It is important to note that in the earliest stages of the disease, before a patient becomes cirrhotic, HCV is usually asymptomatic and patients will likely not experience any HCV-related loss of income. As more severe symptoms begin to present themselves, patients may not be able to maximize productivity. Therefore, we assumed that patients in stages F3 or above experience loss of income if they are not treated or treated and fail treatment. For example, the annual household income is multiplied by the decrement in utility experienced in stage F3 (1-0.801). This is assumed for stages F4, decompensated cirrhosis, hepatocellular carcinoma and liver transplant. In this manner, the loss of income is reflective of the severity of the disease state in which it occurs.

To allow for the possibility of more severe symptoms of complications in the earlier stages of the disease, we conducted a separate societal subgroup analysis that included indirect costs in the same manner for stages F0-F2. We conducted a sensitivity analysis that had a fifteen-year time horizon to better capture the time period over which health systems or health plans makes budgetary and coverage decisions.

We assumed that transition probabilities to more severe disease stages, after treatment failure, were the same as if a patient were not treated. Without cure, HCV progresses naturally.

We assumed that once a patent achieved cure in a given stage of disease, they remained in that cured state (i.e. F0 SVR, F1 SVR, etc.) or can progress. The likelihood of progression after achieving cure is small in comparison to progression if a patient is either not treated or fails on treatment – these parameters are varied in the sensitivity analyses. The impact of treatment is accounted for in the significant reduction in health state costs and increase in health state utility in the cured state. As described above, these are tailored to the specific state.

We assume that only patients in stages F3 or above, those who are cirrhotic are annually screened for liver cancer in accordance with the KPMAS HCV care pathway. Cirrhotic patients are at higher risk for liver cancer and so this annual screening has been implemented for these patients.

Software Used

We used the TreeAge Pro 2017 modeling software to build and analyze this model. The software's various capabilities allowed us to explore our research question via various types of sensitivity analyses.

Results

Our findings are fairly consistent with the current literature, however, we interpret our results in the larger context of the health care setting we studied. We highlight the various aspects of the two perspectives in an impact inventory below. From the health care sector perspective, we include both longevity and health-related quality-of-life effects in the form of QALYs. We did not include other health effects such as secondary transmission of the HCV infection. We include direct health care costs – paid for by traditional third-party payers – as medical costs. We include some future related medical costs such as liver cancer screening, liver enzyme tests and other annual monitoring tests. Although we did not include patient out-of-pocket costs, KPMAS has a Medical Financial Assistance program that helps patients pay for medication.

We value unpaid caregiver-time as informal health care costs and annual lost income in the societal perspective analysis. We did not value patient-time or transportation costs in our analysis. We do know that KPMAS serves patients in both urban and rural settings and provides patients with transportation assistance if necessary; however, we did not value patient time or transportation costs. We did not have access to these costs. In comparison to the largest costs in this model, DAA drug costs, these were likely minimal.

We did not include other non-health care sector costs in the analysis from the societal perspective. It is reasonable to believe that by successfully treating chronic HCV there are positive spillover effects in the legal or criminal justice, social services, and education sectors of the economy.

Impact Inventory

Impact Inventory				
Sector	**Type of Impact (list category within each sector with unit of measure if relevant)**	**Included in This Reference Case Analysis From…Perspective?**		**Notes**
		Health Care Sector	Societal	
Formal Health Care Sector				
Health	Health Outcomes (effects)			
	Longevity effects	✓	✓	Quantity of Life (QALYs)
	Health-related quality-of-life effects	✓	✓	Quality of Life (QALYs)
	Other health effects (eg, adverse events and secondary transmissions of infections)	✗	✗	
	Medical Costs			
	Paid for by third-party payers	✓	✓	All direct health care costs
	Paid for by patients out-of-pocket	✗	✗	Total drug costs
	Future related medical costs (payers and patients)	✓	✓	Costs of liver screening, liver enzyme tests and other monitoring tests
	Future unrelated medical costs (payers and patients)	✗	✗	
Informal Health Care Sector				
Health	Patient-time costs	N/A	✗	*KPMAS serves both rural and urban areas across the three states it serves. Patients do often need assistance getting to and from their providers; KPMAS does provide some transportation assistance. However, we did not have access to this information from the health system - limitation of our analysis. These costs are minimal in comparison to the main driver of the results - DAA costs.
	Unpaid caregiver-time costs	N/A	✓	We assign the caregiver costs according to the hourly wage of home health aides (BLS)
	Transportation costs	N/A	✗	*KPMAS serves both rural and urban areas across the three states it serves. Patients do often need assistance getting to and from their providers; KPMAS does provide some transportation assistance. However, we did not have access to this information from the health system - limitation of our analysis. These costs are minimal in comparison to the main driver of the results - DAA costs.
Non-Health Care Sectors (with examples of possible items)				
Productivity	Labor market earning lost	N/A	✓	Based on national median annual household income (can compare to MD, DC and VA specific median annual household income)
	Costs of unpaid lost productivity due to illness	N/A	✗	
	Cost of uncompensated household production	N/A	✗	
Consumption	Future consumption unrelated to health	N/A	✗	
Social Services	Cost of social services as part of intervention	N/A	✗	
Legal or Criminal Justice	Number of crimes related to intervention	N/A	✗	
	Cost of crimes related to intervention	N/A	✗	
Education	Impact of intervention on educational achievement of population	N/A	✗	
Housing	Cost of intervention on home improvements (eg, removing lead paint)	N/A	✗	
Environment	Production of toxic waste pollution by intervention	N/A	✗	
Other (specify)	Other impacts	N/A	✗	

Reference Case Analysis

The base case analysis, from the societal perspective, showed that the universal treatment option was cost saving and more effective compared to the three other strategies (Table 2, Figure 2). The 'Treat F1+' strategy ($50,231, 28.7 QALYs) cost an additional $98.06 and yielded 0.14 fewer QALYs. Further, the "Treat F2 and above'

strategy ($50,663, 27.28 QALYs) cost an additional $529.91 and yielded 1.43 fewer QALYs. These incremental differences are quite small in comparison to the 'Treat F3-F4' treatment policy. This restrictive access policy ($70,401, 25.21 QALY) costs an additional $20,267.55 and yields 3.49 fewer QALYs per person. The willingness-to-pay line in Figure 2 intersects the 'Treat All' strategy – this provides a visual identification of the optimal strategy from this analysis.

We arrived at the same conclusions from the health care sector perspective (Table 3, Figure 3), although the incremental differences varied between perspectives. The universal treatment policy, or 'Treat All,' was, again, cost saving ($43,350, 28.71 QALYs). The 'Treat F1+' policy ($43,446, 28.57 QALYs) cost an additional $96.56 and yielded 0.14 fewer QALYs. Further, the 'Treat F2+' policy cost an additional $505.69 and yielded 1.43 fewer QALYs. The biggest difference in these results between the health care sector and societal perspectives was the incremental costs and effects between the 'Treat All' policy and the most restrictive 'Treat F3-F4' policy. The most restrictive policy ($55,090, 25.21 QALYs) costs an additional $11,740.64 and yields 3.49 fewer QALYs. This lower incremental increase in cost reflects the exclusion of indirect costs that accrue in later, more severe stages. Once again, the willingness-to-pay slope intersects the 'Treat All' approach to help visually identify the optimal treatment strategy.

In both of these analyses, we saw small differences in costs and QALYs between the 'Treat All' and 'Treat F1+' policies. As per common practice by hepatologists, patients in stages F0 and F1 are often treated as one group given difficulties in differentiating between no fibrosis and minimal or mild fibrosis.

Deterministic Sensitivity Analysis

We come to similar conclusions from the one-way sensitivity analyses from both perspectives – the base-case cost-effectiveness results were robust regardless of variations in any model input. Tornado diagrams (Figures 4a-4g) show the most influential parameters for each comparison from both perspectives

When assessing overall deterministic sensitivity, the tornado diagram shows that the cost of the drug regimen yielded the widest range of expected net monetary benefits, but does not change the overall conclusion of the analysis. Variations in the probability of cure after disease scores F1 – F3 showed the next largest changes in net benefits, but did not change the overall conclusion of the analysis. Figure 5a shows the remaining parameters tested

in this analysis induce minimal variation in the resulting net benefits. None of this variation is enough to change the optimal strategy. Each pairwise comparison below shows the impact on the ICER between the two strategies.

Tornado Diagram: Treat F3-F4 vs. All (Societal)

As the cost of the drug increases from the lower bound, of $0, to the upper bound, $94,500, the ICER increases (Figure 4b). It is not surprising that the parameters that create the most variability in the ICER are those that characterize health state F3. Treating all patients would be beneficial if the cost and utility burden of reaching stage F3 are substantial. None of these variations change the ICER enough to change the optimal strategy.

Tornado Diagram: Treat F2+ vs. All (Societal)

In this comparison, we see that the cost of the drug, the probability of cure after stages F2 and F1 and the health state cost of F2 and F1 yielded the most variation in the base case ICER (Figure 5c). However, none of variation in these model inputs changed the optimal strategy.

Tornado Diagram: Treat All vs. F1+ (Societal)

The drug cost of the regimen creates the largest range in the ICER, but does not change the optimal strategy in this particular comparison. As the probability of cure from fibrosis stage of F0 increases from 0.85 to its upper bound of 1.0, the ICER becomes positive – changing the optimal policy from cost-saving to cost-effective (Figure 5d). However, none of these were large enough to change the decision.

Tornado Diagram: Treat F1+ vs. F2+ (Societal)

The cost of the drug, as expected, creates the largest range in the ICER for this comparison (Figure 5e). As the cost of the drug increases to the upper bound, it changes the 'Treat F1+' policy from cost-saving to cost-effective, but does not change the conclusion of the analysis (Figure 5e). However, these changes were small and not enough to change the best strategy from Treat F1+ to Treat F2+.

Tornado Diagram: Treat F3-F4 vs. F2+ (Societal)

The ICER for this treatment comparison was robust to variations in model parameters (Figure 4f). None of the parameter variations yielded a change in strategy. The most influential parameters include the annual health state cost of stage F3 and the cost of the drug regimen. The 'Treat F2+' was the optimal strategy.

Tornado Diagram: Treat F3-F4 vs. F1+ (Societal)

The ICER for this treatment strategy comparison is also robust to the parameter variations. The most influential parameters in this comparison include the cost of the drug regimen, annual health state cost of stage F3 and the probability of cure after stages F3 and F2 (Figure 4g). The cost of the drug regimen induces the largest range in the ICER. It is reasonable that these parameters shift the ICER – the cost and utility burdens in stage F3 are integral in making this decision between the most restrictive and least restrictive of strategies.

Tornado Diagrams: Health Care Sector Perspective

The series of one-way sensitivity analyses on the net benefits, from the health care sector perspective, show that variation in the drug cost is the primary parameter that induces any shift in expected value (Figure 5a-5g). This is the large upfront investment a health system or payer has to make and therefore it is reasonable to believe that this parameter induces the greatest variation in the resulting ICER. This finding is consistent with current literature.

In addition to the DAA drug regimen cost, the health state cost of fibrosis stage F3 shifted the ICER when comparing any strategy to the 'Treat F3-F4' option. In some comparisons, the change in the drug cost was enough to move the optimal policy choice from cost saving to cost-effective, but not enough to change the decision altogether (Figures 5b-5d). These results are quite similar to the one-way analyses conducted from the societal perspective.

Two-Way Sensitivity Analyses

We assessed the robustness of our base case result to variations of pairs of parameters. Drug cost was the most influential of the parameters in the one-way sensitivity analyses, yet even the large range we used was not enough to change the optimal strategy choice from the base case analysis. The two-way sensitivity analyses similarly demonstrate that the 'Treat All' policy is still the optimal strategy (Figure 6a-6c, Figure 7a-7c).

Threshold Analysis

We conducted a threshold analysis from both healthcare sector and societal perspectives (Tables 4-5). Specifically, we allowed the cost of the drug to vary between the lowest, generic prescription cost, $4, to the highest list price of the drugs available, $94,500. From the societal perspective, we found the dollar threshold to be $36,561.94 – above which Treat F2+ is the optimal strategy and below which the Treat All policy is the dominant approach (Table 4). From the health care sector perspective, we find a similar threshold although the dollar threshold is about $461 less than that from the societal perspective (Table 5). It is reasonable to expect that when the analysis is focused on just costs faced by the health care sector, that threshold would be lower. From the societal perspective, there are many other costs that the drug works to avoid – loss of income or caregiver time – and so it is still valuable to pay that slightly higher price up front. Essentially, we find that if the price were decreased to around $36,000, universal treatment is reasonable and cost-effective. This is promising considering the $26,500 list price of the latest drug that entered the market in August 2017.

Probabilistic Sensitivity Analysis

The overall results of the PSA are best represented by cost-effectiveness acceptability curves (CEAC) that show the probability of each strategy being cost-effective over a range of willingness-to-pay thresholds. We ran 10,000 simulations in this analysis based on distributions of parameters (Table 1).

Societal Perspective

At the $0/QALY threshold, where the decision becomes a cost-minimization problem, the 'Treat F2+' strategy was cost-effective in about 58% of the iterations (Figure 8, Table 6). The 'Treat F1+', 'Treat All' and 'Treat F3-F4' were each cost-effective in 19%, 18% and 2% of simulations, respectively. At the $10,000/QALY threshold, the 'Treat F2+' strategy is cost-effective in about 1% of the simulations. The 'Treat All' and 'Treat F1+' policies were cost-effective in 57% and 41% simulations. As the WTP threshold increased to $200,000/QALY, the universal treatment strategy was cost-effective in about 70% of simulations. Simultaneously, the 'Treat F1+' strategy is cost-effective in about 30% of simulations at the $200,000/QALY threshold. The probability that the universal treatment

policy is cost-effective reaches 70.3% at the $100,000/QALY threshold and is consistently at this level through higher thresholds.

The distribution of the simulations across the 'Treat All' and 'Treat F1+' strategies is consistent with how hepatologists often approach patients with fibrosis scores of F0 or F1. Patients with fibrosis scores of F0 or F1 are often treated similarly – or as patients with the same magnitude of fibrosis. According to HCV experts, it is very difficult to say with certainty that a patient has no fibrosis simply because the tests used to determine magnitude of liver scarring are not sensitive enough to differentiate between these two scores. F0 and F1 patients are often grouped into one category and so the more realistic comparison, as is demonstrated by payer and health system decisions, is between the 'Treat All' and 'Treat F2+' category.

Health Care Sector Perspective

From the health care sector perspective, we excluded productivity losses and the cost of informal caregivers. In the probabilistic sensitivity analysis, at the $0/QALY threshold, the 'Treat F2+', 'Treat F3-F4', 'Treat All' and 'Treat F1+' strategies were cost-effective in 37%, 49%, 4% and 8%, respectively (Figure 10, Table 7). At the $10,000/QALY threshold, the distribution of the simulations appears to approach a similar breakdown as seen in the PSA from the societal perspective. At the $100,000/QALY and $150,000/QALY thresholds, the 'Treat All' strategy is cost-effective in about 70.1% of iterations, while the 'Treat F1+' strategy is cost-effective in 29.8% iterations. When the curves approach the $200,000/QALY threshold, the 'Treat All' strategy becomes cost-effective in 70.4% of iterations and the 'Treat F1+' strategy is cost-effective in 29.6% of iterations. Although the difference is incredibly small, there is slightly more certainty in the optimal strategy from the health care sector perspective.

Incremental Cost-Effectiveness Scatterplots

The incremental cost-effectiveness (ICE) scatterplots (Figures 9a-9f, Figures 11a-11f) demonstrate the results of the probabilistic sensitivity analysis for comparisons between each pair of strategies. Each dot on these plots represents the result of one of the simulations from the probabilistic sensitivity analysis. The WTP threshold, $150,000/QALY, is plotted on each of the graphs so we can visualize its relationship to each simulation

Societal Perspective

The ICE scatterplots for most of these comparisons provide results that yield choices that are quite clear. All simulations either fall completely below the WTP threshold diagonal or above the diagonal. Specifically, when comparing any treatment policy to the most restrictive policy, Treat F3-F4, the simulations demonstrate that any other policy is recommended over this approach (Figures 9a, 9d, 9e). However, the comparison between the 'Treat All' and 'Treat F1+' strategy (Figure 9c) produces a scatterplot that further demonstrates the uncertainty we saw in the CEAC. The results from each of the simulations in this plot fall in each of the four quadrants. This plot, again, demonstrates the physiological similarity between the F0 and F1 health states discussed above.

Health Care Sector Perspective

As expected, the conclusions from the ICE scatterplots from the health care sector perspective are similar to those from the societal perspective (Figure 11a-11f). From this perspective, when we compare Treat F1+ or the Treat All strategies to the current health system treatment strategy, Treat F2+, the results show that expanded treatment is recommended over Treat F2+ (Figures 11b, 11f). However, when Treat F2+ is compared to Treat F3-F4, Treat F2+ is the cost-effective option. Again, we see the one pairwise comparison that presents with uncertainty, with simulation results falling in all quadrants of the cost-effectiveness plane, is the between the 'Treat F1+' and the 'Treat All' strategy (Figure 11c). It remains that expanding the treatment from the current strategy, treating F2 and above, is the optimal strategy recommendation.

Value of Information Analysis

From the societal perspective, the average, or expected value of information from all 10,000 iterations from the PSA, is $7,750.98 (Table 8). Having 'perfect information' on the uncertain parameters in our model is worth $7,750. The EVPI and the WTP have a positive relationship – as the WTP increases, the value of perfect information increases (Figure 12). These results tell us how much we, as a society, would need to invest in more research around the parameters in the model, per person, in order to increase the confidence with which we identify a treatment strategy as optimal. At the $150,000/QALY threshold, if we were to invest about $7,750 in research per person with HCV in the United States, we could be more certain around treatment recommendations. More research

could be done on any of the parameters used in the model – for example, if we could determine, exactly, the probability of cure for every treated patient, we could increase societal net benefit from the optimal strategy.

We draw similar conclusions from the health care sector perspective (Table 9). However, the EVPI at the $150,000/QALY threshold is $7,269.29 – this lower cost of additional information is reflective of the slightly higher certainty we observed in the cost-effectiveness acceptability curve from the health care sector perspective. The EVPI increases as the WTP increases, with the exception of a dip in EVPI at about $20,000/QALY (Figure 13). This dip in the EVPI at the $20,000/QALY threshold reflects the greater certainty at the lower WTP thresholds in the CEAC. The more certainty around the optimal strategy decision, the lower the cost of additional information to reach 'perfect' information or determining the optimal strategy with 100% probability. The more certain we are from the probabilistic sensitivity analysis, the less benefit there is to be gained from more investment in research.

Important to note is that there is an average decrease in incremental cost and an average increase in incremental effect if we were able to remove all uncertainty.

We've made some assumptions around indirect costs in our model including who requires caregiver time and incurs losses in income. Specifically, the model assumes that patients with a fibrosis score of F3 or above incur loss of income and those with a fibrosis score of F4 or above require informal, round-the-clock, care. There is certainly some possibility that patients with lower fibrosis scores may need to take time away from work or require informal assistance in their home due to other complicating comorbidities or debilitating symptoms – it may not be as systematic. Symptoms or complications will vary from patient to patient and it is generally unpredictable how severe the symptoms of the infection will be and how quickly they will manifest in each patient. Increasing certainty in these parameters would increase the confidence with which the model identifies an optimal strategy.

Subgroup Analysis - Testing Assumptions Around Indirect Costs

While patients in the earliest stages of the disease are mostly asymptomatic, we can never know with certainty the disease experience of each individual patient. As we did before, we linked the magnitude of loss of income to the decrement in utility experienced in a state from 'perfect health' (1 – the utility of a given state). We, again, included the annual cost of informal care in the pre-treatment stages of F0, F1, F2 and F3. We included an

annual cost of informal care for the these stages after SVR – the annual cost was reduced by an amount proportional to the increase in health state utility achieved after cure.

We rule out the 'Treat F3-F4' treatment policy by extended dominance – it is the least effective strategy of the four options (Table 10, Figure 14). The remaining three less restrictive options remain cost-effective – making the optimal strategy unclear in the base case analysis. The universal access policy, 'Treat All,' yielded the greatest effect but at the greatest cost. The 'Treat F2+' strategy was the least costly of all treatment options, but did not yield the largest effect. If we compare all other strategies to 'Treat F2,' we still find that all of our options fall well under the $150,000/QALY threshold, however the 'Treat F3-F4' is cost-saving.

The CEAC demonstrates the uncertainty in the optimal strategy, which changes and is dependent upon the WTP-threshold (Figure 15, Table 11). We find much greater uncertainty about the optimal strategy than in the primary analysis. Up to the $30,000/QALY threshold, the 'Treat F2+' strategy was cost-effective in 100% of simulations. As the WTP threshold increases from $30,000/QALY to $100,000/QALY, the 'Treat F1+' becomes the best strategy with 100% of simulations showing it to be the cost-effective option. After the $180,000/QALY threshold, the probability that 'Treat F1+' option is cost-effective steadily decreases, while the 'Treat All' option steadily increases in likelihood of cost-effectiveness.

At both the $150,000/QALY and $200,000/QALY thresholds, the 'Treat F1+' is the optimal treatment strategy. We are not surprised by these results given that there are now greater costs associated with treating even the mildest stages of disease at the same thresholds we used in the primary analysis.

The value of information analysis (Figure 16, Table 12) reflects the varying levels of certainty shown in the CEAC. At the $60,000/QALY threshold, there is a large expected value of perfect information since the simulations were split across two strategies making the optimal strategy uncertain. Between $100,000/QALY and $200,000/QALY, the expected value of perfect information is essentially $0 – the 'Treat F1+' strategy was cost-effective in 100% of simulations so there is no added benefit to having additional, perfect information.

When we compare this version of the societal perspective to the health care sector perspective, the conclusions vary – the optimal strategy from the societal perspective is 'Treat F1+', while the optimal strategy from the health care sector perspective is to 'Treat All.'

Sensitivity Analysis – Time Horizon from Health Care Sector Perspective

When we limited the time horizon of the model to 15 years, we found that both the 'Treat All' and 'Treat F2+' strategies were cost-effective (Table 13, Figure 17). The 'Treat All' strategy was the most expensive in terms of lifetime costs ($36,256.98) but yielded the greatest lifetime effects (14.77 QALYs). While the 'Treat F2+' was the least expensive with a lifetime cost of $34,658.01, it yielded fewer QALYs. The shorter horizon limits the time over which health gains can develop and our analysis indicates this restrictive strategy as potentially optimal.

The probabilistic sensitivity analysis resulted in some differences of certainty at the lower end of the WTP threshold range (Figure 18). For example, at $0/QALY, the 'Treat F3-F4' strategy is cost-effective in 85% of the simulations, while 'Treat F2+' is cost-effective in the remaining 15%. At the $20,000/QALY threshold, there is a much greater uncertainty. As the WTP threshold increases through $150,000/QALY and above, the 'Treat All' policy is cost-effective in about 70% of the simulations while 'Treat F1+' is cost-effective in the other 30% (Figure 19). This is similar to what we found in the 30-year time horizon from the health care sector perspective.

Strengths & Limitations

Our analysis has several key strengths that set our study apart from what has already been done in the literature. First, we derived key parameters from a real-world population and not national estimates. Specifically, the initial distribution of patients across fibrosis scores and cure rate were derived from the Kaiser Permanente study sample from a previous analysis. Using a measure of effectiveness improves the applicability of the results over current studies that must rely of clinical trial data. Finally, we incorporated the follow-up regimen from KPMAS' care pathway to structure the model in a system-specific way.

While we include these key parameters from the KPMAS perspective, an important limitation of this analysis is the lack of system-specific values that would influence the parameters included in the cost-effectiveness model. The KP system incorporates quality of care metrics and patient satisfaction into their payment model which differs greatly from other fee-for-service reimbursement mechanisms. This study was not necessarily designed to include the unique features and payment models of the integrated health care system. Future research in this area could engage the stakeholder more in the building of the model and interpretation of results. The non-specific health care costs limit the applicability of the model to any KP system, but increase the generalizability of the results to

other care settings, health plans or systems. While we modeled several important components of a cost-effectiveness analysis, we did not include system-specific details like costs. Assuming unmeasured factors are equal across scenarios, we demonstrate that our results are robust to variation in model parameters.

As in most cost-effectiveness models, we made a series of assumptions. To account for losses in productivity, we use the national annual median household income to increase generalizability. However, the patients from the KPMAS study sample from which we draw some of our data reside in Maryland, Washington D.C., or Virginia – each with higher median household incomes than the national estimate. Increasing the potential lost income would likely favor the less restrictive strategies. Further, we assumed that only the most severely ill patients require constant informal care. Specifically, the symptoms increase in severity upon the development of cirrhosis. We feel comfortable in these assumptions as we consulted with a hepatology expert to provide insight into the impact of the disease given their experience with the disease. Finally, we did not include transportation or patient time costs as part of informal health care sector costs. We know that patients in KPMAS' rural service areas may require assistance with transportation and the exclusion of these costs is a limitation of this analysis. They are certainly an important part of assessing access to care, however, in this model, the magnitude of these costs would be minimal in comparison to the overwhelmingly large costs of the drug regimens.

We did test the assumptions around who could incur indirect costs in the model. When we allow patients in all fibrosis stages to incur indirect costs, the optimal strategy from the societal perspective becomes the 'Treat F1+' strategy. This is not surprising, as now society will face more costs earlier in the course of the disease. Payers make budgetary decisions on a shorter time horizon and so we varied the time horizon to better reflect this process.

Finally, we did not construct an infectious disease model. Incorporating potential for transmission as well as potential for prevention would likely increase the value of DAA treatment – from both perspectives.

Policy Implications & Discussion

Our analysis is just one piece of a large policy discussion that is taking place across the country. While the incredibly high list prices of the novel chronic HCV treatments have become the epitome of the drug pricing issue in the United States, their impact on access to prescription drugs has become an issue across many clinical contexts. For example, the new PCSK9 drugs to treat high cholesterol, a chronic condition, have list prices on the order of

$20,000. While this is 'small' in comparison to the prices of Harvoni, for chronic HCV, patients are on cholesterol medication for life substantially increasing the cost facing patients and payers. In a short 8 or 12 weeks, patients could be cured of a potentially fatal disease. This is what sets DAAs, for chronic HCV, apart from the rest of the specialty drugs. The medical breakthrough in the American health care setting is even more important given the rise in Hepatitis C cases due to injection drug use.

The American Association for the Study of Liver Diseases has stated that DAAs are the new standard of care and all patients diagnosed with HCV should be treated with these drugs. However, the high list prices set by manufacturers have made it difficult for payers and systems to make treatment accessible to all patients – the response to prices varies across setting. Most private payers are able to cover the regimen for all their patients. While KPMAS treats its more severe patients immediately [133], in a previous analysis of this study sample, we did not find a difference in fibrosis score distribution across treatment status. This is likely because patients who are initially monitored can be treated for different reasons after seeing the primary care physicians – abnormal test results or complicating comorbidities. KP also may provide financial assistance to patients who require assistance paying for HCV medication. The annual monitoring of less severe cases allows providers to promptly link patients to treatment when they see clinical changes in the patient.

State Medicaid programs initially had the most restrictive policies [63] – including disease severity, sobriety requirements, specialty prescriber – but have eased these over time at the strong recommendations of providers and lawsuits. The Veteran's Administration, covering a population in which chronic HCV is prevalent, as of 2016, has been covering the drug regimens for all patients regardless of disease severity. Medicare has also been covering DAA regimens for its patients, however, although cured from the infection, patients who age into Medicare eligibility with HCV may have progressed to the more severe stages of the disease. After developing cirrhosis, patients need to be monitored for the liver cancer or kidney disease – this public payer faces this cost burden.

This study adds to the body of evidence that restricting access to DAA therapy to only the more severely ill patients (F3-F4) is not the optimal strategy. [94, 99, 105, 106, 109, 110, 192, 193] We do find, that depending on the assumptions we make around indirect costs, the magnitude of treatment expansion – to what fibrosis score – varies.

One major change in the treatment landscape from the time the KPMAS study sample was drawn is the recently approved, pan-genotypic therapy, Mavyret, from the pharmaceutical manufacturer Abbvie. The list price of

Mavyret is $26,500 – a 70% reduction from the $94,500 list price of Harvoni. Further, Mavyret is approved for an eight-week regimen. At the time our study sample was drawn from the Hepatitis C registry, ledipasvir/sofosbuvir was the preferred, and most widely used, DAA regimen for patients. The price that a health plan pays for the drug is an important factor and so we varied this using a wide range in the sensitivity analysis ($4 - $94,500).

Abbvie's strategic pricing of Mavyret in late 2017 will likely cause a shift in the DAA market. While Harvoni may still be preferred for HCV genotype 1 by physicians, insurers and health systems may now have some leverage with which to negotiate. Our threshold analysis demonstrated that we are indifferent between the two strategies 'Treat All' and 'Treat F2+' when the drug costs $36,000 at the WTP threshold of $150,000/QALY. If payers choose Mavyret as their preferred therapy, they may negotiate reimbursement at an even lower rate.

Legislative efforts to battle high drug prices have been underway. Vermont, for example, has enacted transparency legislation that required drug makers to justify any price hikes. [213] Maryland recently enacted anti-gouging legislation in which manufacturers can be penalized for "unconscionable increases" in prices for essential generic drugs. [214] A major development in the discussion around high drug prices includes the recent report (December 2017) published by the National Academies of Sciences, Engineering and Medicine titled "Making Medicines Affordable: A National Imperative." [215] The committee highlights the fundamental tradeoff that leads to high prices – investing in research and development is extremely costly, but without the investment, patients, in the future, will miss out on potential new and improved drugs. The committee sums up the issue in the following way: "drugs that are not affordable are of little value, and drugs that do not exist are of no value." [215]

Conclusion

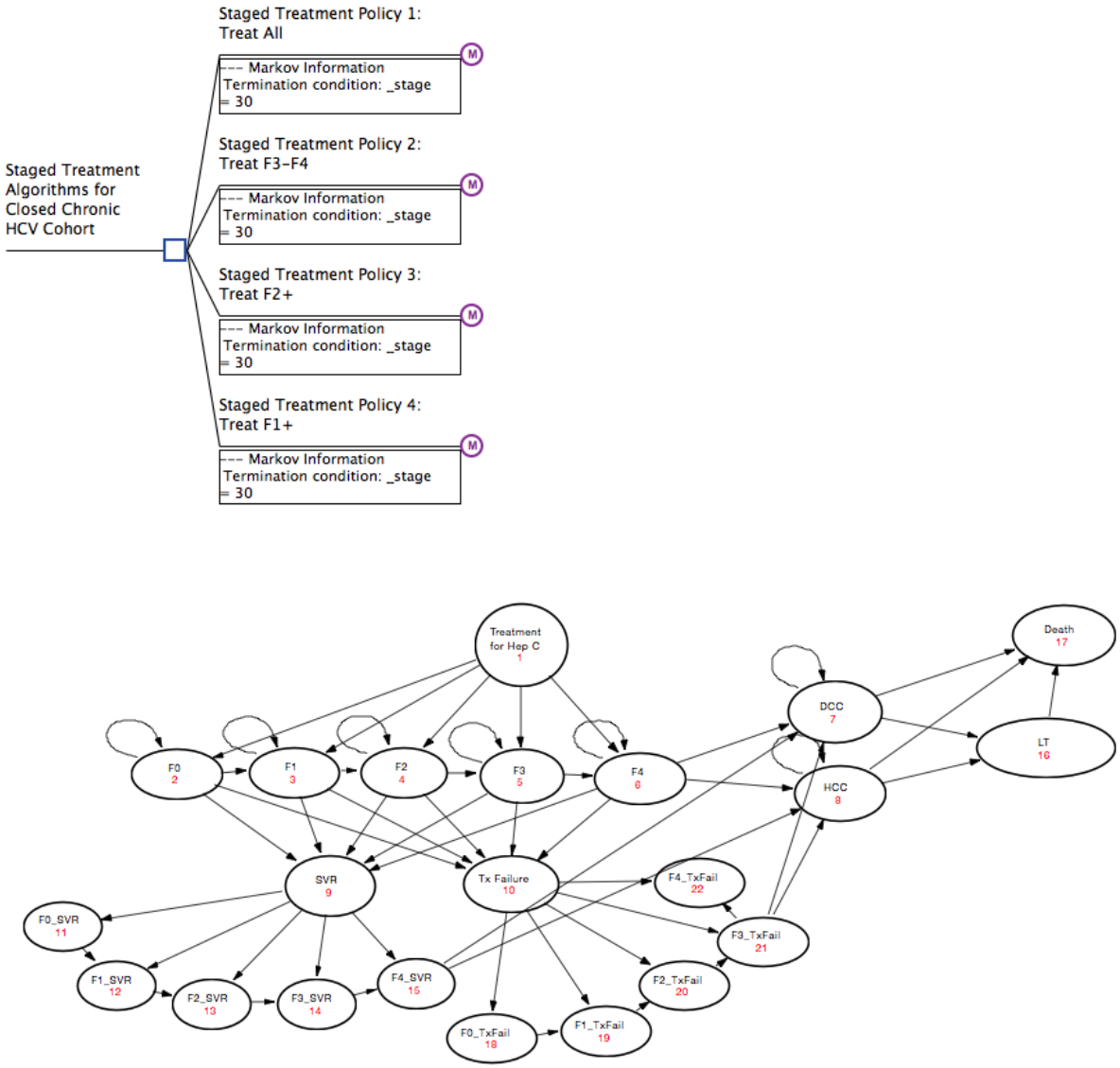
This analysis clearly demonstrates that expanding access to DAA treatment for patients at any stage of chronic HCV is the cost-effective, potentially cost-saving, strategy for the health system to treat their HCV population. We show that the choice of this optimal strategy is robust to variations in model parameters as demonstrated by both deterministic and probabilistic sensitivity analysis. The 'Treat All' strategy is in line with the recommendations from the national clinical guidelines.

Health systems such as KPMAS are in a unique position to engage HCV patients into treatment promptly. The value of the optimal strategy lies in the long-term cost savings – payers and systems must reconcile the tradeoffs

between upfront investments and long-term pay-offs, using innovative reimbursement models, within the context of their chronic HCV population.

Tables & Figures:

Figure 1: Model Schematic



Notes: Each of the four branches represents a treatment policy we evaluated in the cost-effectiveness analysis (top). The health state diagram (bottom) shows the natural progression of chronic HCV as well as the states they may reach after DAA treatment success or failure.

Table 1: Summary of Model Parameters

Table 1 - Hepatitis C Cohort Characteristics, Disease Progression Parameters, Mortality Rates, Costs, Utilities			
Description of Parameters	**Distribution**	**Reference**	**Notes**
Incidence of Disease Across Fibrosis Stage	Dirichlet (LIST(A;B;C;D;E))	KPMAS Study Sample	Refers to # of patients with this F-score in analysis from Aim 1
Transition Probabilities	Beta (95% CI, SE); Uniform (+/-25%)	Literature; Assumptions	Probability of death (CDC), Probability of transition after cure (Assumption -proportion of transition probability before Tx), Transition from state to state (Literature)
Effectiveness of Drug	Beta (95% CI, SE)	KPMAS; Literature	Cure rate calculated from study sample in Aim 1; SA distribution from published data on clinical trials
Health State Costs	Gamma (95% CI, SE)	Literature; Assumptions	Annual Health State Costs (Literature); Annual health state costs after cure (proportion of health state costs prior to treatment, based on disease severity)
Drug Costs (DAA)	($4-$94,500)	Literature, RedBook	Variation captured fluctuations in the market and range of list prices of drugs currently on the market
KPMAS Tests and Monitoring Costs	Min/Max; Uniform	Literature, Assumptions	Costs of certain lab tests and screening for follow-up (treated) and monitoring (not treated)
Median Annual Household Income	Uniform (+/-25%)	Kaiser State Health Facts	National Median Annual household Income for generalizability
Indirect Costs - Loss of Income	-	Based on Median Annual household Income	Linked to median annual household income and vary along with that parameter value; (1-utility of health state) * median income
Cost of Informal Care	Uniform (+/-25%)	Based on BLS Home Health Aide Hourly Wage & Literature	Estimated using 2016 hourly wage of home health aide; study estimating hours of informal care necessary by disease severity
Indirect Cost - Informal Caregiver Time Costs	-	Based on Cost of informal care parameter	Estimated as follows: (cost_informalcare - (cost_informalcare*(utility of cure state - utility of health state))); varies along with informal care cost parameter
Health State Utilities	Uniform (Min/Max)	Literature	Utilities for pre-treatment and in the cured states come from studies in the literature that have elicited preferences in HCV

Table 2: Base Case Analysis (Societal)

	Strategy	Lifetime Cost	Incremental Cost	Lifetime Effects	Incremental Effect	ICER	NMB
Societal Perspective	**Dominant**						
	Treat All	**50133.56**		**28.71**			**4255893**
	All Referencing Common Baseline						
	Treat All	50133.56		28.71			4255893
	Treat F1+	50231.62	98.06	28.57	-0.14	-726.27	4235541
	Treat F2+	50663.47	529.91	27.28	-1.43	-370.72	4040951
	Treat F3-F4	70401.11	20267.55	25.21	-3.49	-5801.44	3711594

Figure 2: Base Case Analysis CEA Plot (Societal)

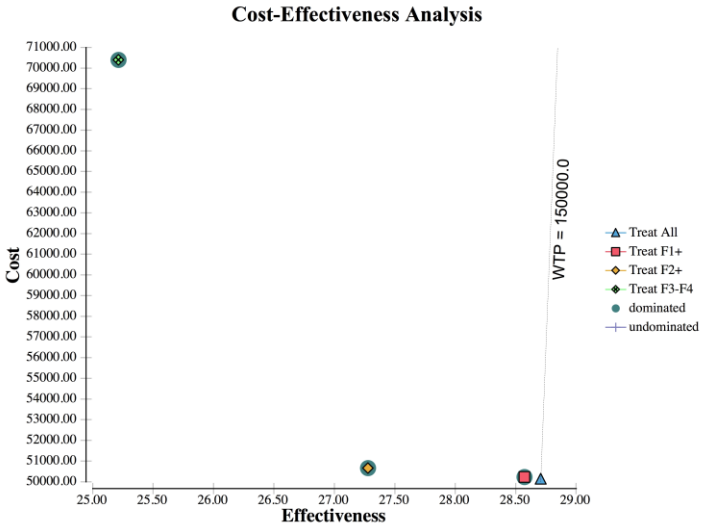
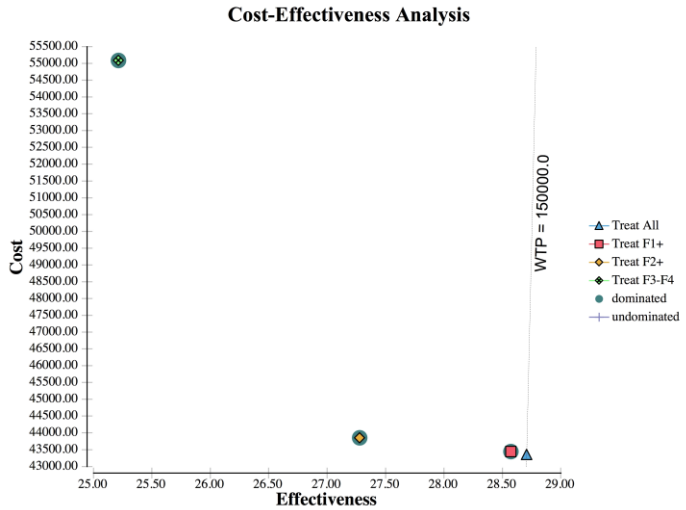


Table 3: Base Case Analysis CEA Text Report (Health Care Sector)

	Strategy	Lifetime Cost	Incremental Cost	Lifetime Effects	Incremental Effect	ICER	NMB
Health Care Sector Perspective	**Dominant**						
	Treat All	**43350.34**		**28.71**			**4262676**
	All Referencing Common Baseline						
	Treat All	43350.34		28.71			4262676
	Treat F1+	43446.9	96.56	28.57	0.14	-715.16	4242326
	Treat F2+	43856.03	505.69	27.28	-1.43	-353.77	4047758
	Treat F3-F4	55090.98	11740.64	25.21	-3.49	-3360.67	3726904

Figure 3: Base Case Analysis CEA Plot (Health Care Sector)



Notes: The WTP threshold line at $150,000/QALY intersects the optimal strategy in this analysis.

Figure 4a: Tornado Diagram – Net Benefits (Societal)

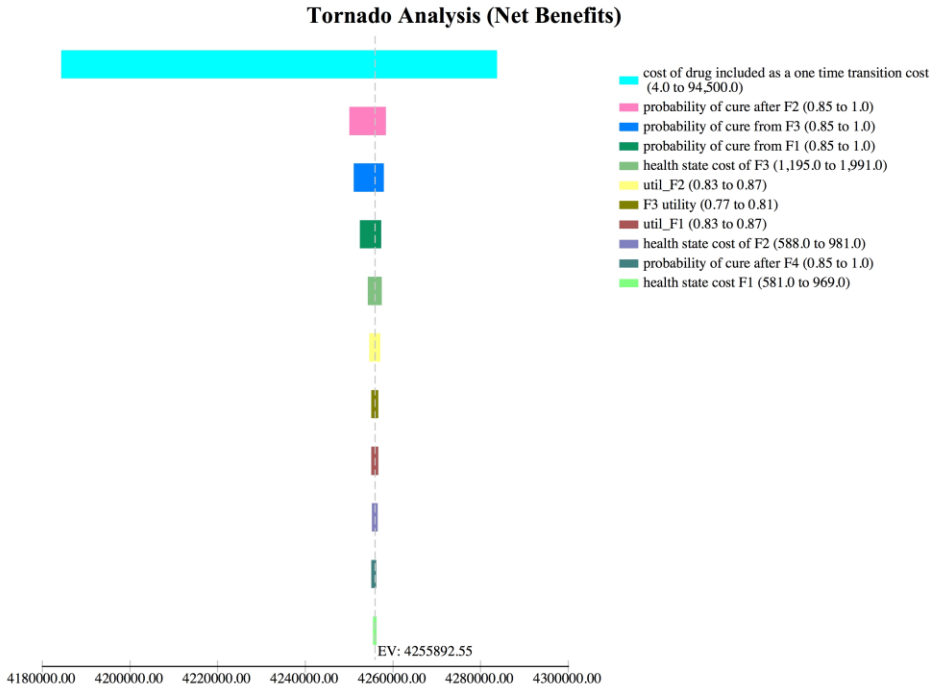


Figure 4b: Tornado Diagram – Treat F3-F4 vs. Treat All (Societal)

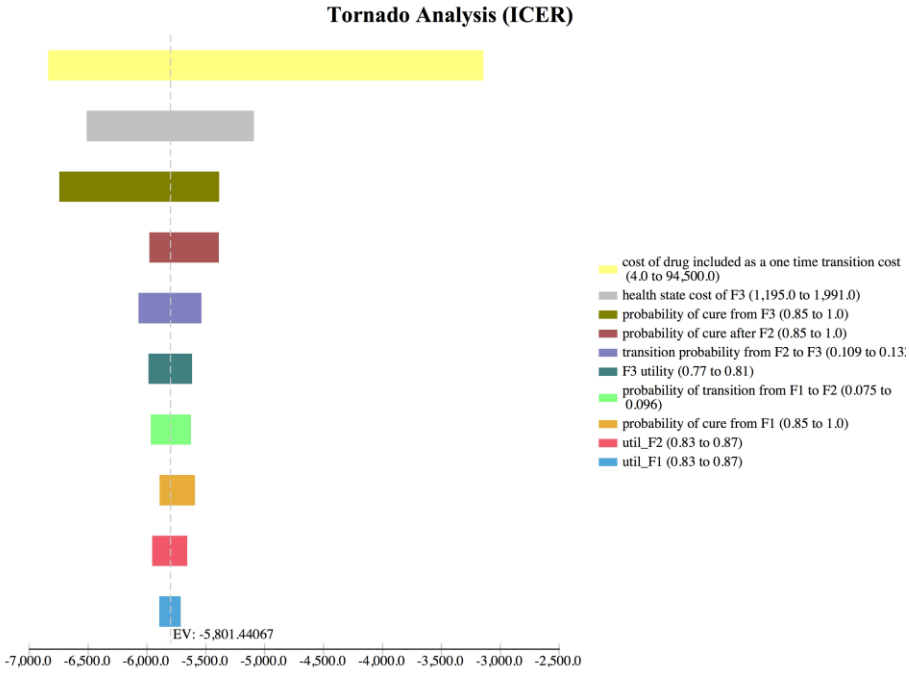


Figure 4c: Tornado Diagram – Treat F2+ vs. Treat All (Societal)

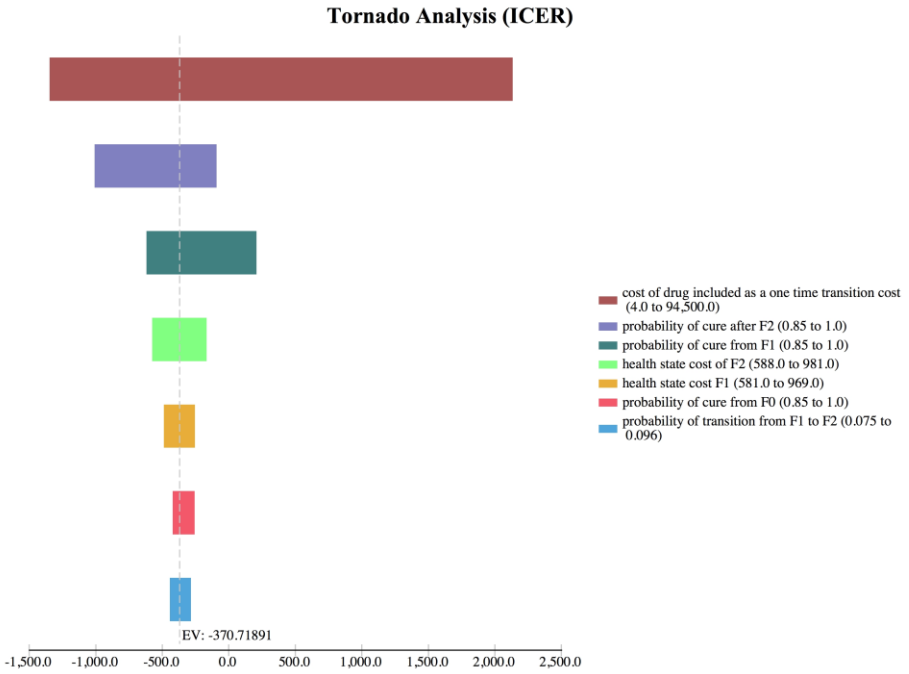


Figure 4d: Tornado Diagram – Treat All vs. Treat F1+ (Societal)

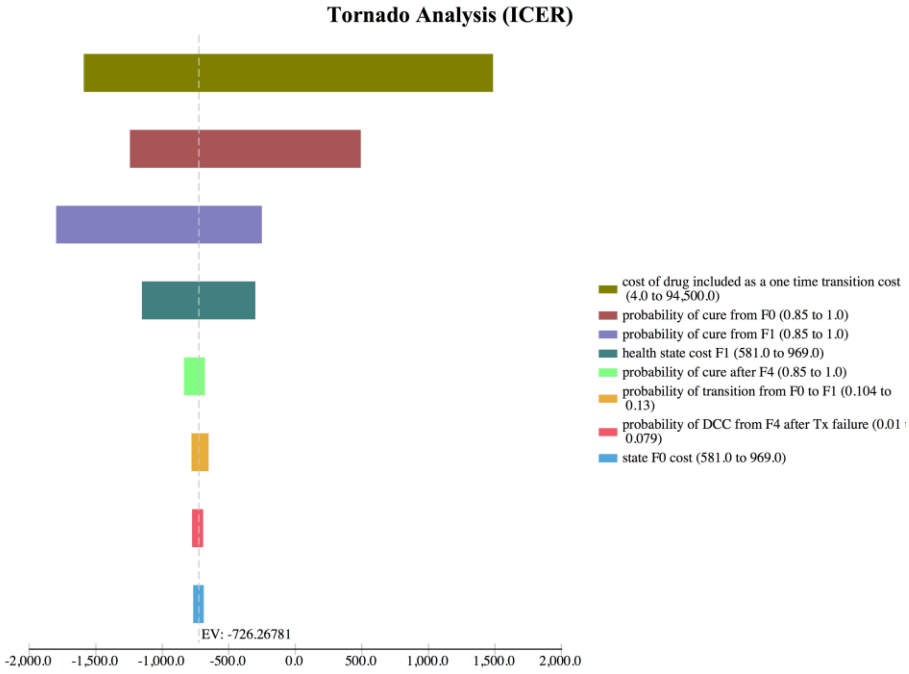


Figure 4e: Tornado Diagram – Treat F2+ vs. Treat F1+ (Societal)

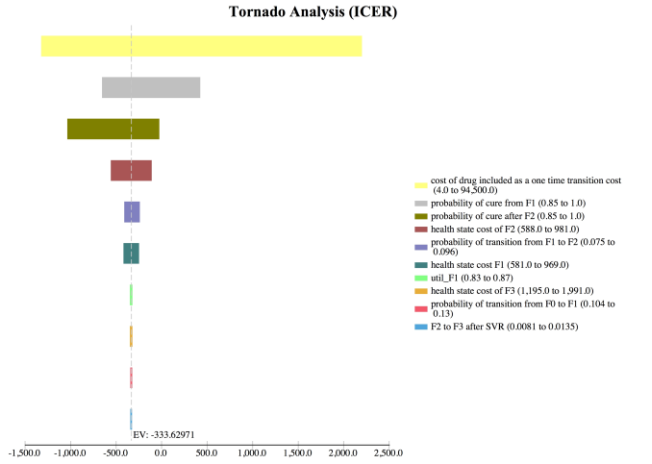


Figure 4f: Tornado Diagram – Treat F3-F4 vs. Treat F2+ (Societal)

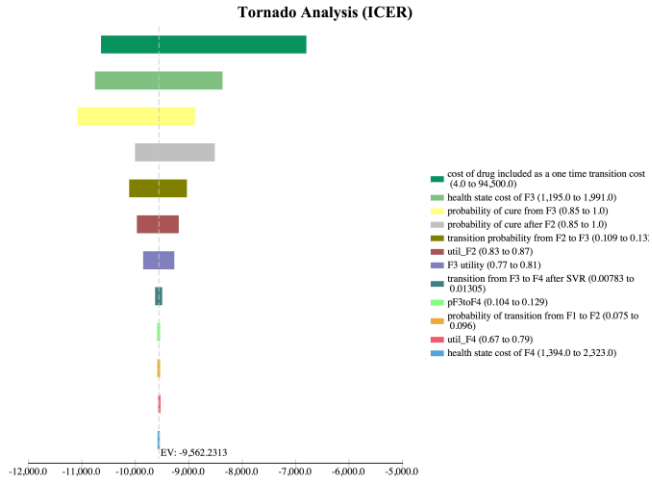


Figure 4g: Tornado Diagram – Treat F3-F4 vs. Treat F1+ (Societal)

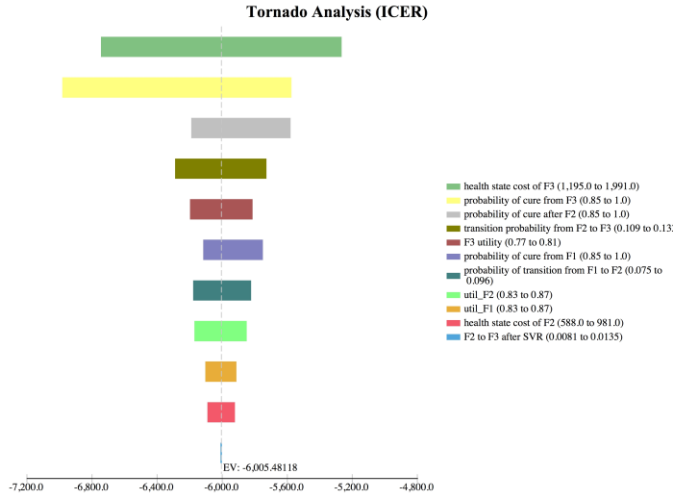


Figure 5a: Tornado Diagram – Net Benefits (Health Care Sector)

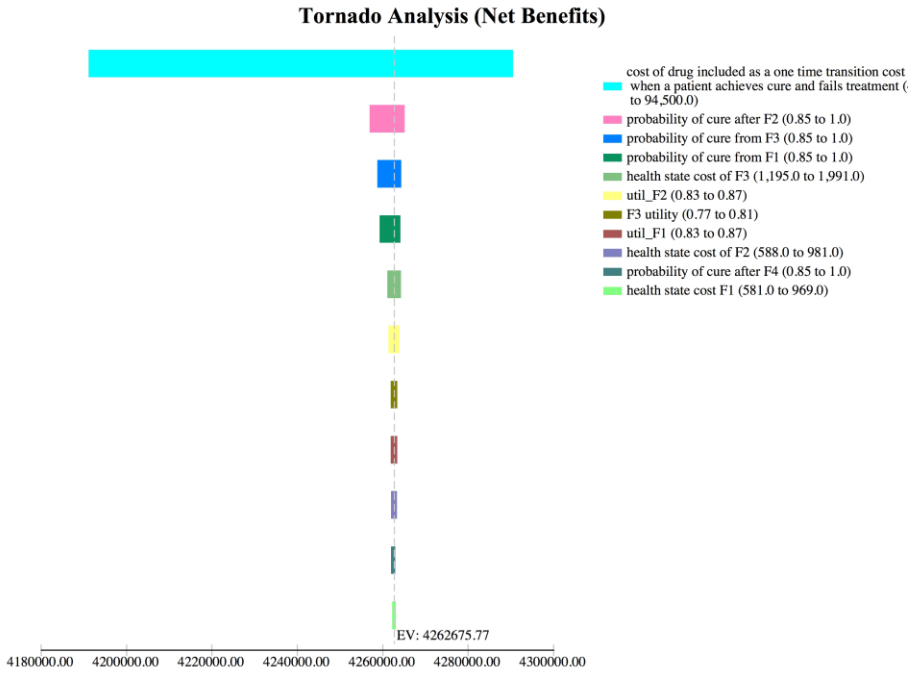


Figure 5b: Tornado Diagram – Treat F3-F4 vs. Treat F2+ (Health Care Sector)

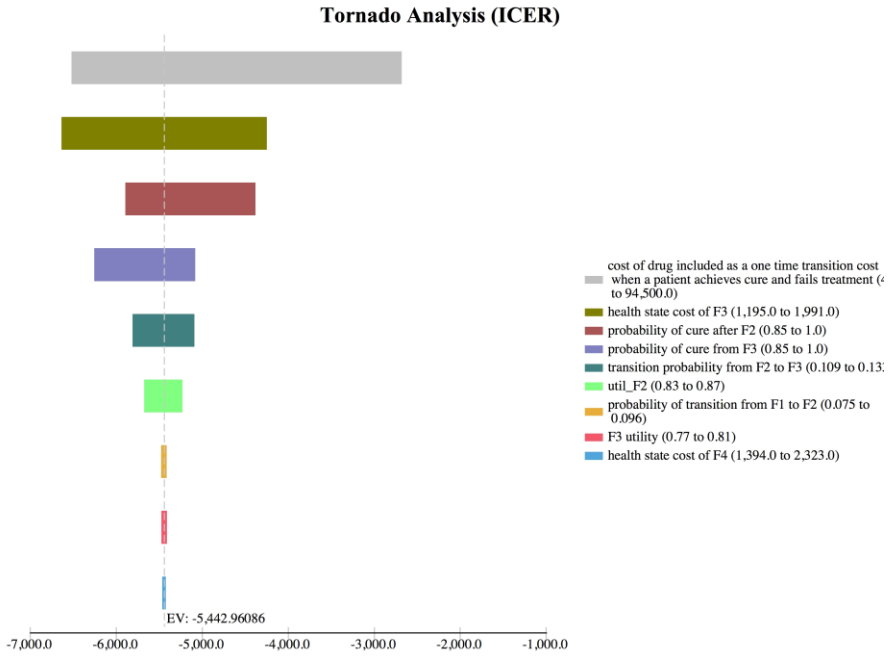


Figure 5c: Tornado Diagram – Treat F3-F4 vs. Treat All (Health Care Sector)

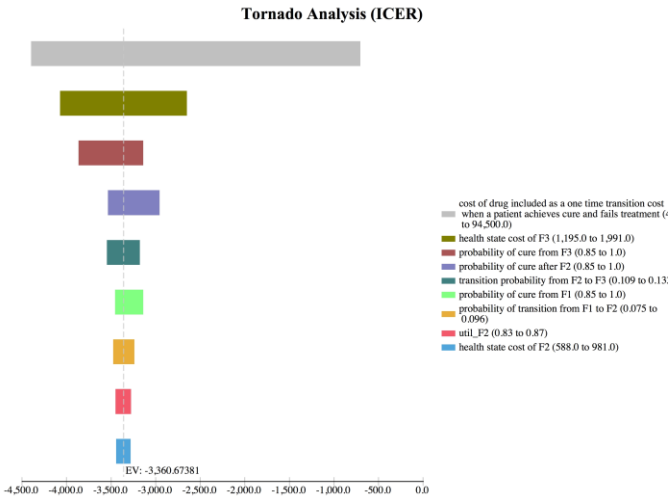


Figure 5d: Tornado Diagram – Treat F3-F4 vs. Treat F1+ (Health Care Sector)

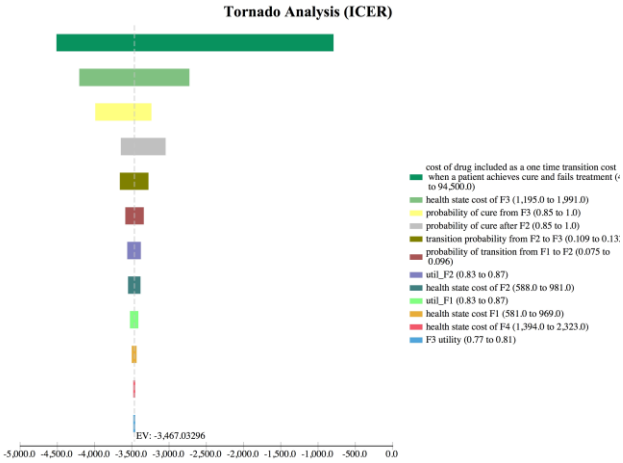


Figure 5e: Tornado Diagram – Treat F2+ vs. Treat F1+ (Health Care Sector)

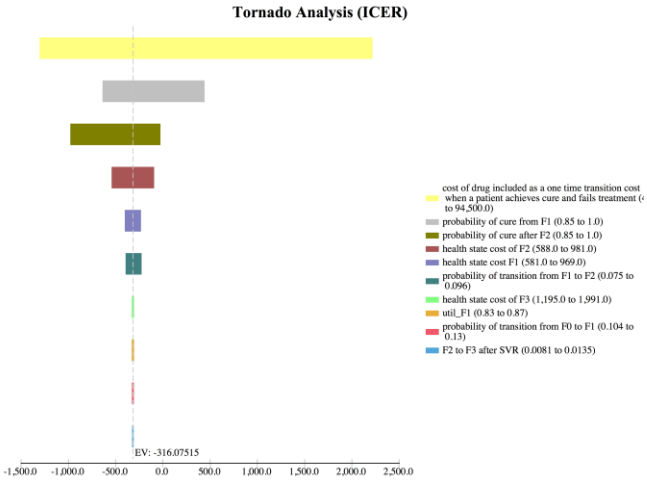


Figure 5f: Tornado Diagram – Treat F2+ vs. Treat All (Health Care Sector)

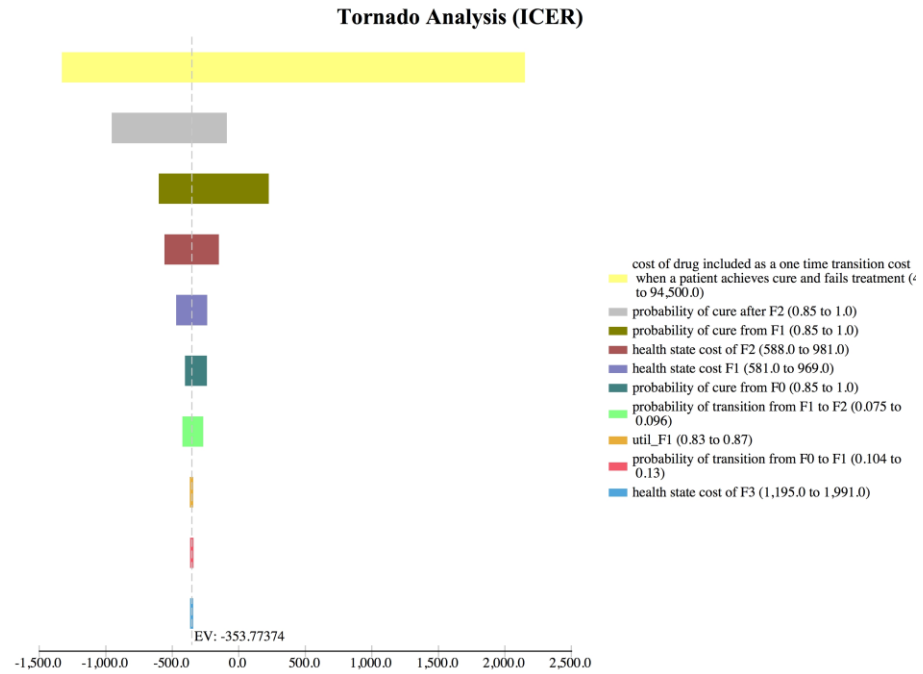


Figure 5g: Tornado Diagram – Treat All vs. Treat F1+ (Health Care Sector)

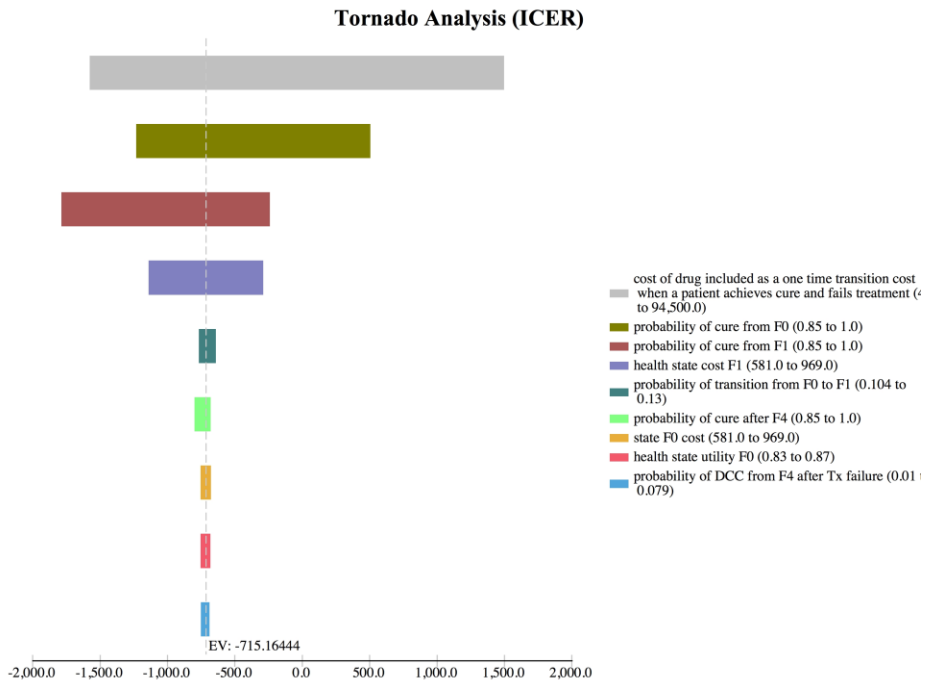


Figure 6a: Two-Way Sensitivity Analysis – Drug Cost vs. F3 Health State Cost (Societal)

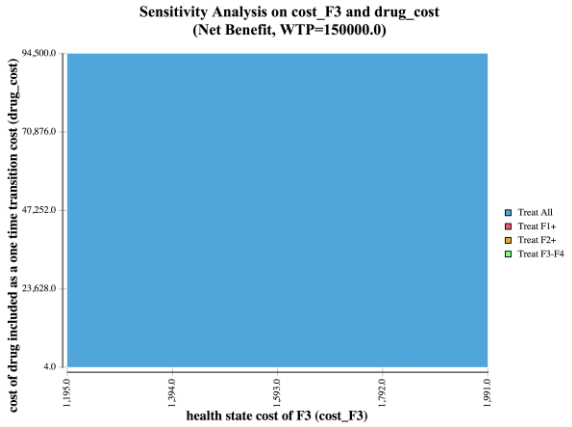


Figure 6b: Two-Way Sensitivity Analysis – Drug Cost vs. Probability of Cure from Health State F3 (Societal)

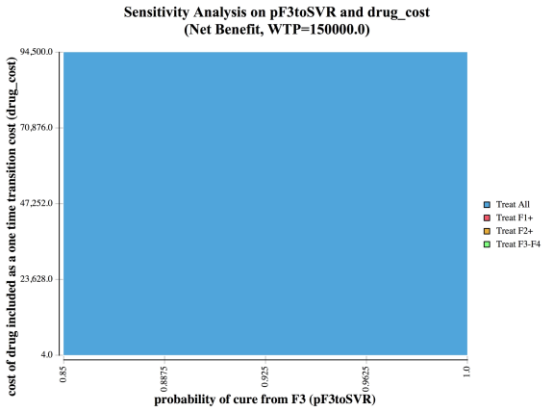


Figure 6c: Two-Way Sensitivity Analysis – Drug Cost vs. Probability of Cure from Health State F2 (Societal Perspective)

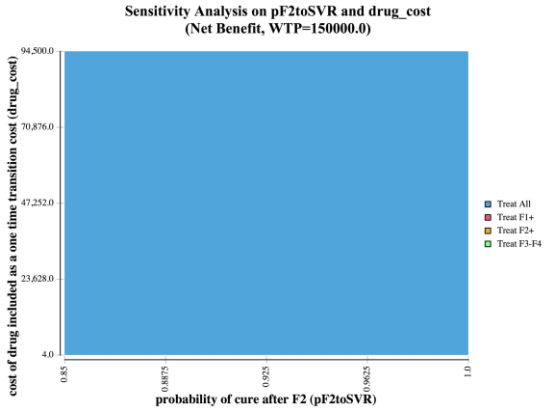


Figure 7a: Two-Way Sensitivity Analysis – Drug Cost vs. F3 Health State Cost (Health Care Sector Perspective)

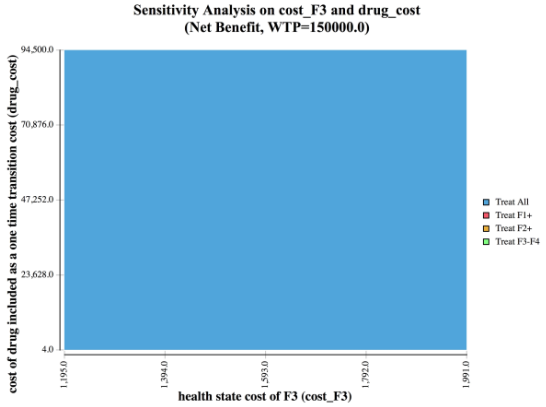


Figure 7b: Two-Way Sensitivity Analysis – Drug Cost vs. Probability of Cure from Health State F3 (Health Care Sector Perspective)

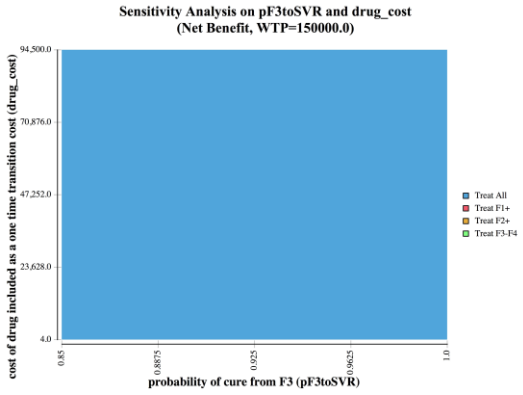


Figure 7c: Two-Way Sensitivity Analysis – Drug Cost vs. Probability of Cure from Health State F2 (Health Care Sector Perspective)

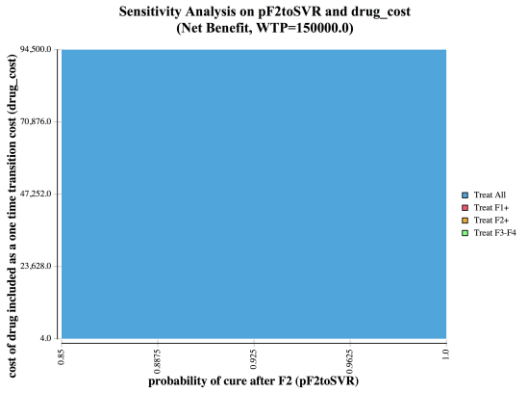


Table 4: Threshold Analysis – Societal Perspective

Societal Perspective Parameter Type	Parameter	Threshold	Strategy 1	Strategy 2	Expected Value	WTP	Maximum Cost of Drug
Cost	drug_cost	36561.94	Treat All	Treat F2+	60717.7381	150000	94,500

Table 5: Threshold Analysis – Health Care Sector Perspective

Health Care Sector Perspective Parameter Type	Parameter	Threshold	Strategy 1	Strategy 2	Expected Value	WTP	Maximum Cost of Drug
Cost	drug_cost	36102.02	Treat All	Treat F2+	53450.7268	150000	94,500

Figure 8: Probabilistic Sensitivity Analysis: Cost-Effectiveness Acceptability Curve (Societal)

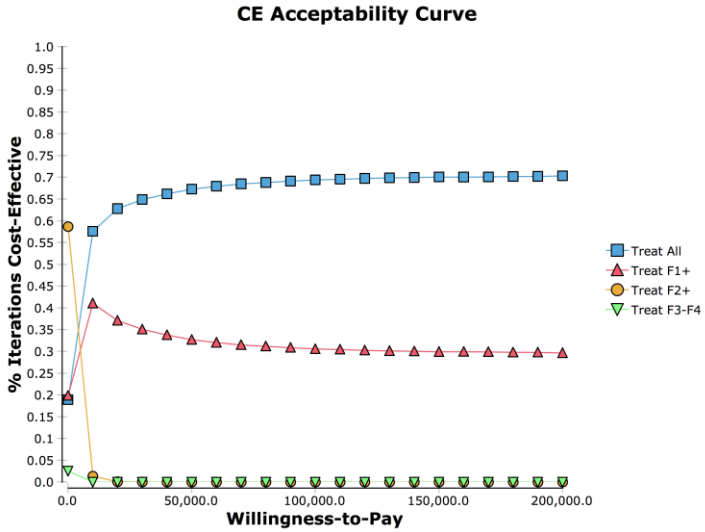


Figure 9a: Incremental Cost-Effectiveness Scatterplot – Treat F3-F4 vs. Treat All (Societal)

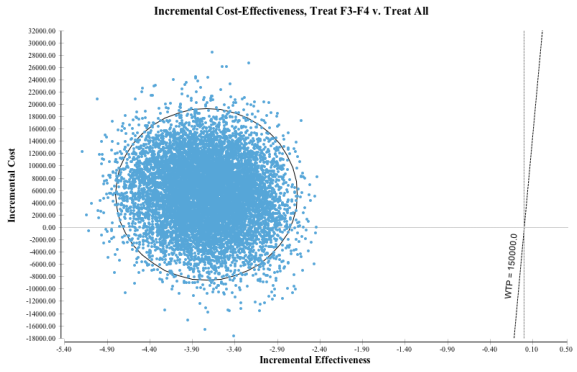


Figure 9b: Incremental Cost-Effectiveness Scatterplot – Treat F2+ vs. Treat All (Societal)

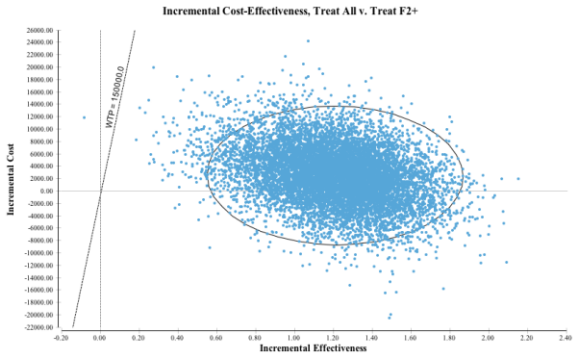


Figure 9c: Incremental Cost-Effectiveness Scatterplot – Treat F1+ vs. Treat All (Societal)

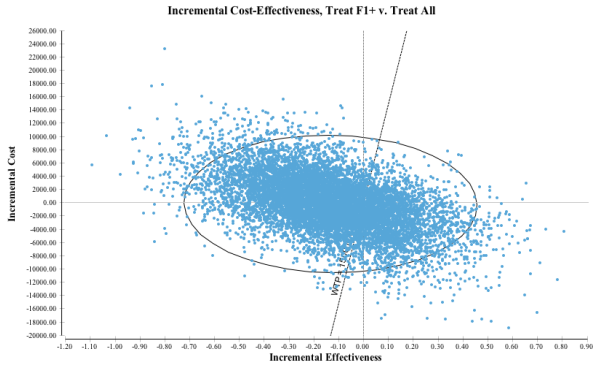


Figure 9d: Incremental Cost-Effectiveness Scatterplot – Treat F3-F4 vs. Treat F2+ (Societal)

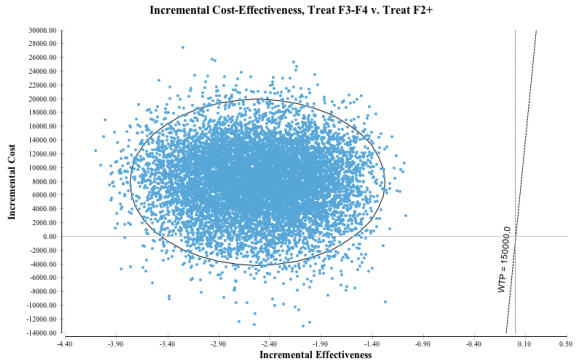


Figure 9e: Incremental Cost-Effectiveness Scatterplot – Treat F3-F4 vs. Treat F1+ (Societal)

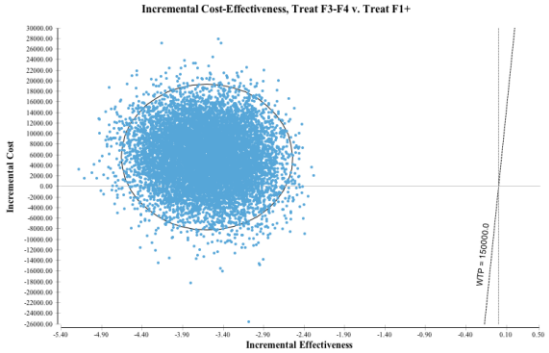


Figure 9f: Incremental Cost-Effectiveness Scatterplot – Treat F2+ vs. Treat F1+ (Societal)

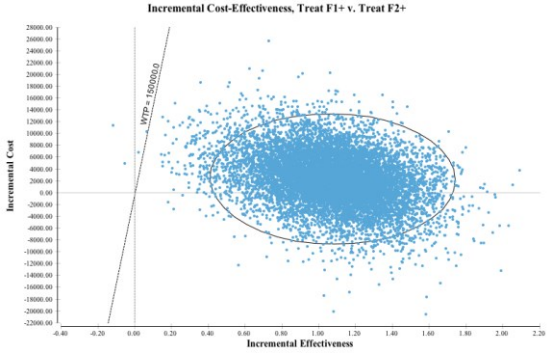


Figure 10: Probabilistic Sensitivity Analysis: Cost-Effectiveness Acceptability Curve (Health Care Sector)

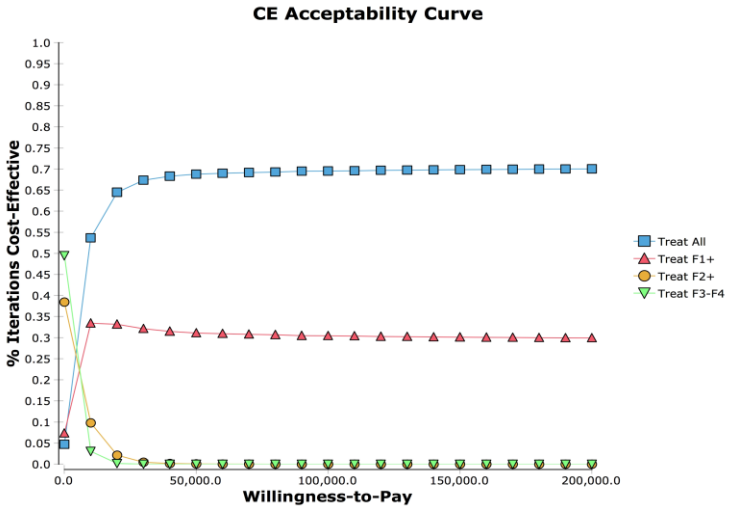


Figure 11a: Incremental Cost-Effectiveness Scatterplot – Treat F3-F4 vs. Treat All (Health Care Sector)

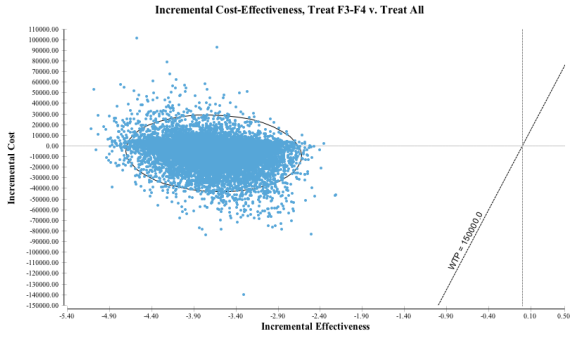


Figure 11b: Incremental Cost-Effectiveness Scatterplot – Treat F2+ vs. Treat All (Health Care Sector)

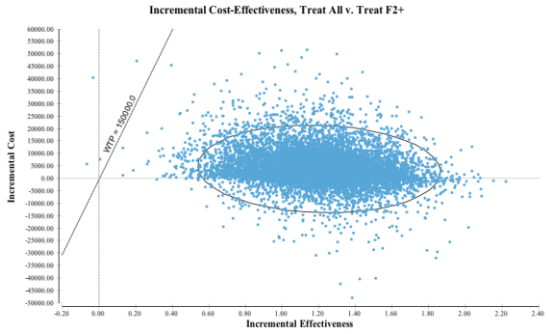


Figure 11c: Incremental Cost-Effectiveness Scatterplot – Treat F1+ vs. Treat All (Health Care Sector)

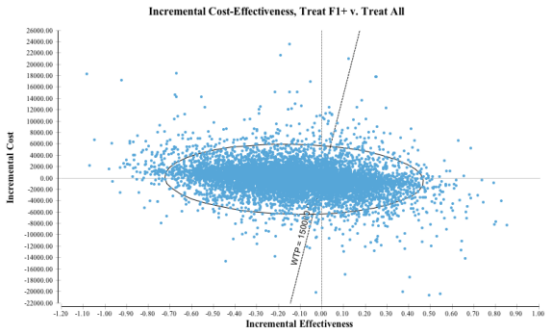


Figure 11d: Incremental Cost-Effectiveness Scatterplot – Treat F3-F4 vs. Treat F2+ (Health Care Sector)

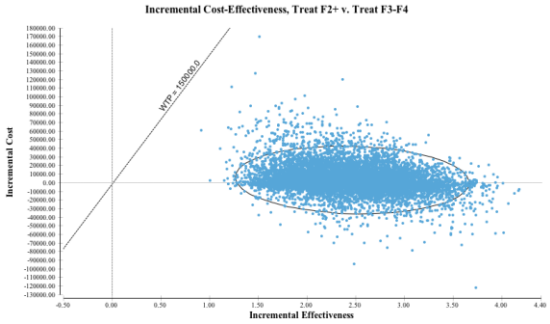


Figure 11e: Incremental Cost-Effectiveness Scatterplot – Treat F3-F4 vs. Treat F1+ (Health Care Sector)

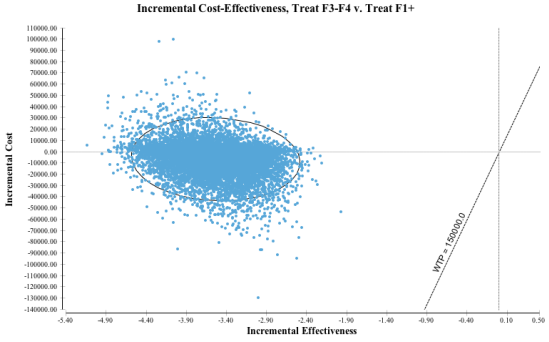


Figure 11f: Incremental Cost-Effectiveness Scatterplot – Treat F2+ vs. Treat F1+ (Health Care Sector)

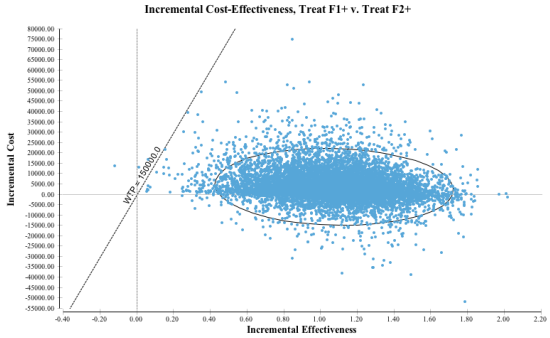


Table 8: Value of Information Summary Text Report (Societal Perspective)

Willingness-to-Pay	EVPI/EVPI (Incremental NMB)	Average Incremental Cost with Perfect Info	Average Incremental Effect with Perfect Info	Optimal Strategy
$150,000/QALY	$7,750.98	-963.15	0.045	Treat All

Figure 12: EVPI vs. WTP Plot (Societal)

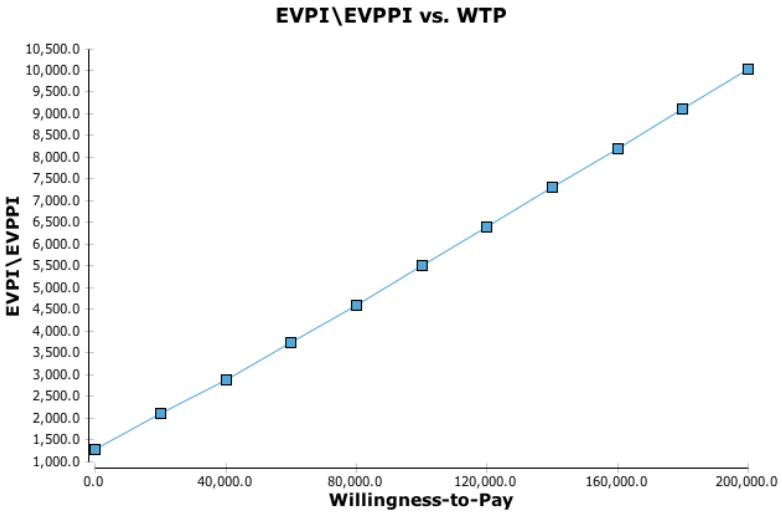


Table 9: Value of Information Summary Text Report (Health Care Sector)

Willingness-to-Pay	EVPI/EVPI (Incremental NMB)	Average Incremental Cost with Perfect Info	Average Incremental Effect with Perfect Info	Optimal Strategy
$150,000/QALY	$7,269.29	-337.4	0.046	Treat All

Figure 13: EVPI vs. WTP Plot (Health Care Sector)

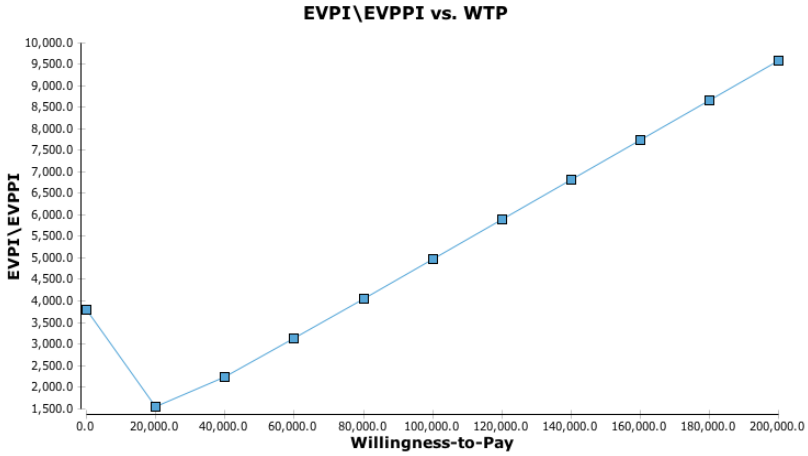


Figure 14: Base Case Analysis CEA Plot (Societal with Expanded Indirect Costs)

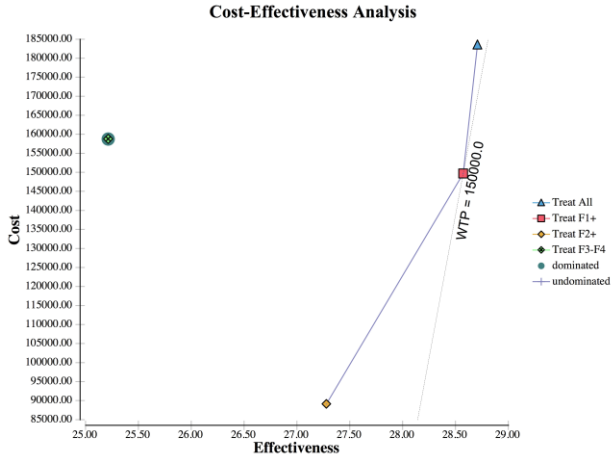


Table 10: Base Case Analysis CEA Text Report (Societal with Expanded Indirect Costs)

Expanded' Societal Perspective - Subgroup Analysis	**Dominant**						
	Treat F2+	**89129.98**		**27.28**			**4002484**
	Treat F1+	**149706**	**60576.12**	**28.57**	**1.29**	**46799.04**	**4136066**
	Treat All	**183535.1**	**33829.09**	**28.71**	**0.14**	**250540.3**	**4122491**
	All Referencing Common Baseline						
	Treat F2+	89129.88		27.28			4002484
	Treat F1+	149706	60576.12	28.57	1.29	46799.04	4136066
	Treat F3-F4	158777.3	69647.38	25.21	-2.06	-33741.8	3623218
	Treat All	183535.1	94405.21	28.71	1.43	66044.75	4122491

Figure 15: Probabilistic Sensitivity Analysis: Cost-Effectiveness Acceptability Curve (Societal with Expanded Indirect Costs)

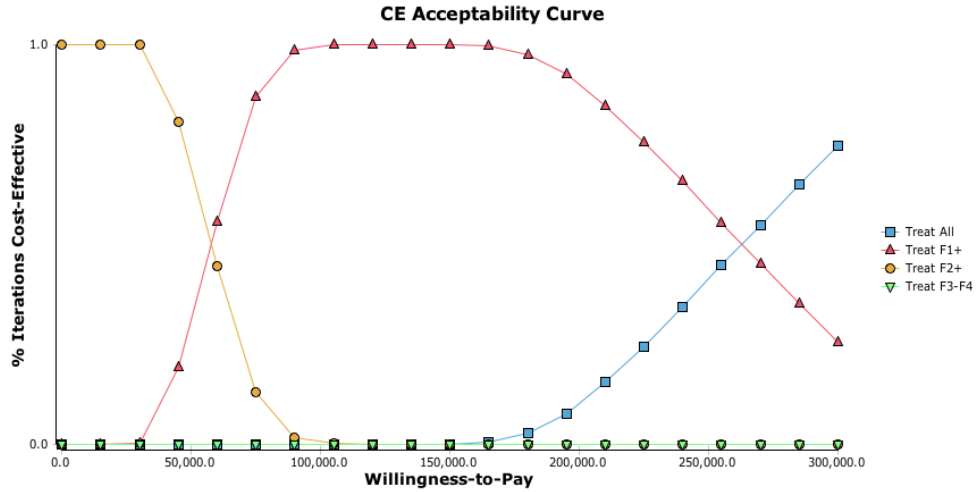


Figure 16: EVPI vs. WTP Plot (Societal with Expanded Indirect Costs)

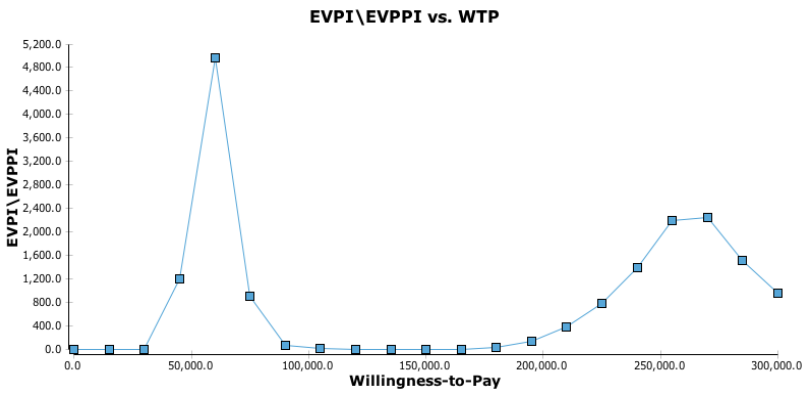


Table 12: Value of Information Summary Text Report (Societal with Expanded Indirect Costs)

Willingness-to-Pay	EVPI/EVPI (Incremental NMB)	Average Incremental Cost with Perfect Info	Average Incremental Effect with Perfect Info	Optimal Strategy
$150,000/QALY	0.21	4.74	0	Treat F1+

Table 13: Base Case Analysis CEA Text Report – Health Care Sector (15 Year Time Horizon)

	Strategy	Cost	Incremental Cost	Effects	Incremental Effects	Incr C/E	NMB	C/E
Excluding dominated								
	Treat F2+	34658.01		14.06			2073622	2465.85
	Treat All	36256.98	1598.97	14.77	0.71	2247.54	2178737	2455.33
All referencing common baseline								
Undominated	Treat F2+	34658.01		14.06			2073622	2465.85
Abs. Dominated	Treat F3-F4	35869.87	1211.86	13.18	-0.88	-1383	1940971	2721.76
Ext. Dominated	Treat F1+	36158.61	1500.6	14.69	0.63	2379.96	2166698	2462.16
Undominated	Treat All	36256.98	1598.97	14.77	0.71	2247.54	2178737	2455.33

Figure 17: Base Case Analysis CEA Plot – Health Care Sector (15 Year Time Horizon)

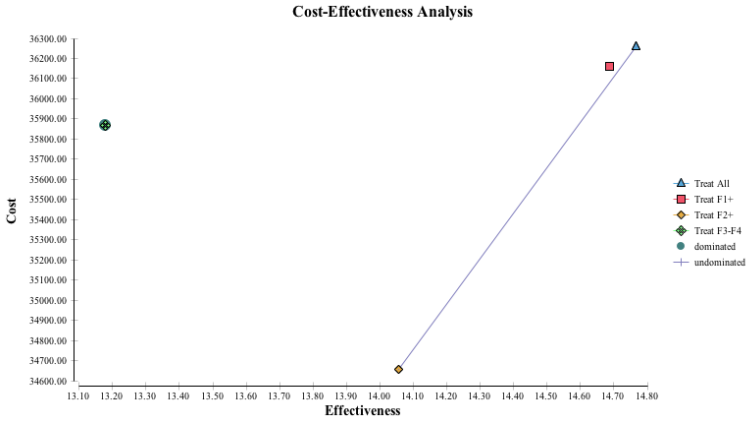


Figure 18: Probabilistic Sensitivity Analysis: Cost-Effectiveness Acceptability Curve (Health Care Sector– 15 Year Time Horizon)

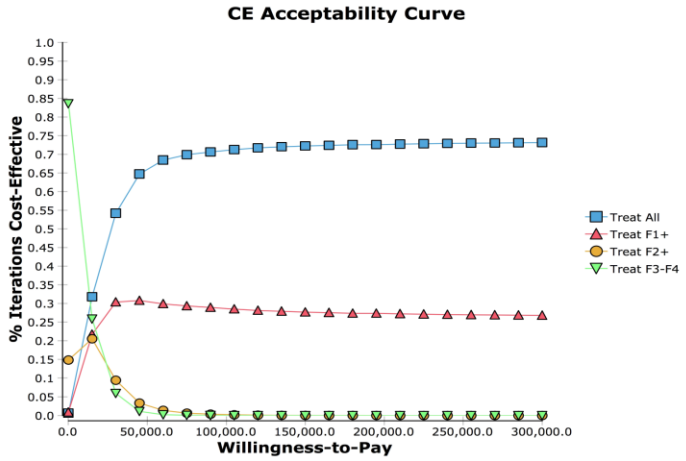
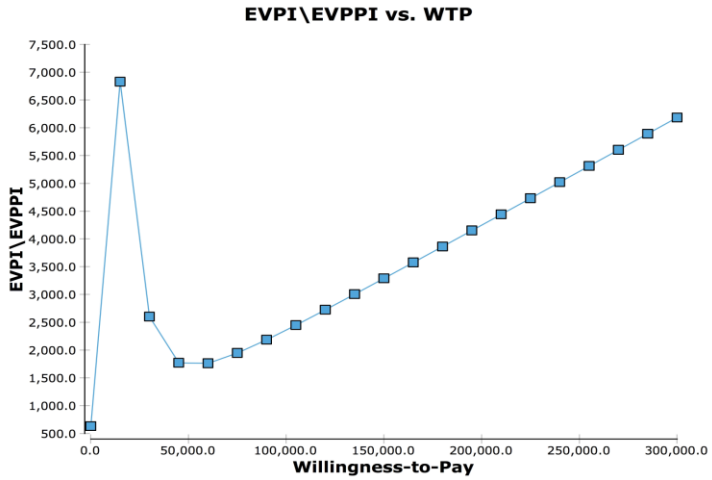


Figure 19: EVPI vs. WTP Plot (Health Care Sector– 15 Year Time Horizon)



Chapter 5: Conclusion

The development of the second-generation direct-acting antiviral (DAA) therapies for the treatment of chronic Hepatitis C virus (HCV) has been touted as a medical breakthrough and marks a pivotal moment in the treatment landscape for this infectious disease. Along with the dramatic increase in cure rates from the DAAs, spending on these HCV antivirals has increased in tandem. Without treatment, about 20% of patients who develop chronic HCV can develop advanced liver disease.

Many in the baby boomer generation are at an increased risk of having chronic HCV due to changes in blood transfusion screening in the early 1990s. Recently, the opioid epidemic in the United States is a significant cause for concern given the transmission of the virus through injection drug use. A CDC report released in May 2017 found that the heroin epidemic in the U.S. has been linked to a surge in Hepatitis C rates – an increase of nearly 300% from 2010 to 2015. [216] Recent studies have also demonstrated that persons who inject drugs do experience high HCV cure rates and the clinical justification for restricting access to treatment for this population is lacking. [1, 217, 218]

The antivirals for the treatment of chronic HCV have become the epitome of a widespread issue in the pharmaceutical market. Manufacturers of these new drugs defend the high prices saying they incorporate the significant value associated with this drug – it cures the infection in 8-12 weeks with a single daily pill. [219] While the value of a cure to a patient with Hepatitis C is almost limitless, a price tag that renders the drug unaffordable to many can diminish that value. Substantial pushback from patients and patient advocacy groups, including lawsuits against payers, has forced easing of coverage restrictions. [70]

Even more striking is that patients in other disease contexts, where care is similarly expensive, are not forced to wait until they can demonstrate more severe illness or overcome multiple, tedious insurance hurdles to receive coverage. [59, 220] For example, oncologic therapies are often priced in the hundreds of thousands of dollars and we don't see explicit triaging of cancer patients. [221] According to the CDC, the lifetime cost of treating HIV is in the hundreds of thousands of dollars. [222] Treatment for HIV, much like that for cancer, is a long-term therapeutic regimen and many individuals are living with the disease.

Again, while this triaging approach to treating HCV is slowly changing, we know that there isn't universal access to treatment. While this study focuses on the chronic HCV context, the analytic and policy discussions are applicable to drug pricing policies across clinical contexts.

Summary of Findings

Aim 1

Our first analysis focused on predictors of treatment. We found, even in an integrated healthcare system with a great deal of care coordination, there are still some differences in access to treatment across age, location of service, and some comorbid conditions including substance use disorders. We also found some differences in likelihood of treatment by case type – incident cases in our sample were more likely to be treated during our study period than prevalent cases. Patients with genotype 1 HCV were also more likely to be treated than patients with genotype 2 or 3 of the virus. Incident cases were immediately "exposed" to the treatment choice set that included the two new DAAs primarily used for treatment during our study period – sofosbuvir (Sovaldi) and ledipasvir (Harvoni). The timing of their diagnosis potentially enabled their connection to treatment to occur almost immediately. These one-time screening guidelines for patients born between 1945-1965 may have also driven our result that patients in the older age categories had an increased likelihood of receiving treatment during our analytic period. The decreased likelihood of receiving treatment for patients with a substance use disorder might be cause for concern. While we did not differentiate between alcohol abuse or other drug use, recent reports from the CDC have shown that with the opioid epidemic, there has been a surge in cases of Hepatitis C. [216] Given the difficulties around diagnosing SUD or the stigma surrounding these conditions, the presence of SUD may have also been underreported in our data. If the differences are even more pronounced than what we found, an integrated system such as KPMAS is well positioned to successfully bring these patients into the care continuum.

We did not find any differences in likelihood of treatment by race. This is important since African Americans experience substantially higher rates of chronic HCV and HCV-related deaths than other ethnic groups. [223] We also did not find any differences in likelihood of treatment by insurance type.

Aim 2

In our second analysis, we explored the value of the new DAAs by assessing the effect of treatment on healthcare resource utilization to quantify potential resource use offsets. The prescription record data from KPMAS provided information on the start and completion dates of each treated patient's DAA regimen. We took advantage of the variation in treatment start dates across patients by conducting a time series analysis to accurately capture the variation in the follow-up periods and measure subsequent resource utilization.

We found that majority of the patients in our study sample were treated in the latter half of the analytic period. In the unadjusted, exploratory analyses, we found different patterns in the utilization of resources depending upon the type of resource – total, ambulatory, inpatient or emergency department. Those treated earlier, on average, used less resources than those who remained untreated. When we moved to the later intervals, we found, on average, more post-treatment use in those that were treated.

In the adjusted longitudinal negative binomial regression models, we found a downward effect of treatment on resource utilization as anticipated given the clinical trial results for DAAs with high cure rates. Patients who were treated experienced lower rates of all types of utilization we explored in this study; however, these results were not statistically significant. We also found, in the ambulatory and emergency department models, that certain intervals during which a patient was treated significantly increased or decreased the rate of outcome utilization.

This analysis was limited in follow-up time. Treatment regimens lasted twelve weeks and we began the post-treatment observation period after the regimen was completed. This limited the follow-up time by an additional three months for treated patients in our study sample.

Aim 3

In our final analysis, in which we assessed the cost-effectiveness of four different treatment policies, we found that expanded access, or universal treatment with DAAs to patients with all fibrosis scores, was the optimal strategy for our health care system audience. The 'Treat All' option was cost-effective, in some cases cost-saving, and well under the willingness-to-pay threshold for the United States setting. In the deterministic analysis from the societal perspective, we found the 'Treat All' option to be cost-saving relative to each of the other policies with a lifetime cost of $50,133.56 and lifetime effects of 28.71 QALYs. We found similar results in the deterministic

analysis from the health care sector perspective except with lower costs since we did not capture any indirect costs here ($43,350.34, 28.71 QALYs). All resulting ICERs were well below the willingness-to-pay threshold of $150,000/QALY from both analytic perspectives. These results were robust to variations in model parameters in both deterministic and probabilistic sensitivity analyses. It is important to note that when we limit the time horizon to 15 years, from the health care sector perspective, we find that the 'Treat All' and 'Treat F2+' strategies were both dominant, or optimal, strategies.

The parameter driving these current policy decisions is the price of the drug - the most recently approved drug, Mavyret, has a list price of $26,500, while Harvoni has a list price of $94,500 for a course of therapy. Although we do not know the exact price that Kaiser Permanente pays for the DAAs after discounts, we varied this parameter substantially to capture the lowest and highest prices possible, however, the optimal strategy remained universal access. Using a value of information analysis, we found that the expected value of perfect information was about $7,000/per patient from both societal and health care sector perspective. By investing these resources, for the HCV population, we could increase our confidence in the optimal strategy recommendation. Finally, a threshold analysis showed that if a health plan could negotiate the price of the drug regimen down to about $36,000, this would make the universal treatment policy the optimal choice over the 'Treat F2+' approach. Given the price of Mavyret is about $10,000 less than this already, health plans will be in a better position to expand access to treatment.

Our Contribution

Researchers are just making a dent in understanding how patients in the new era are being treated with the availability of multiple treatment options and we have taken one of the first steps in providing this information to the wider medical community. This work has provided some insight into how an integrated system may have the resources and structure to ensure minimal to no disparities in treatment decisions.

We found a 95% cure rate in this real-world population – providing strong evidence that these drugs work outside of the controlled environments in which clinical trials are conducted. While every health system or payer treats patients with different clinical profiles, finding similar cure rates to those of clinical trials is important as policymakers and payers navigate the potential move towards value-based reimbursement models. Additionally, we

also found that the likelihood of treatment did not differ based on fibrosis scores, race or insurance status. While other payers and systems may triage their patients according to fibrosis score, KPMAS may be uniquely positioned to link patients to care earlier in their disease process. Although KPMAS has a triaging pattern in place in their care pathway, we don't see that this F-score cut-off is adhered to strictly thereby increasing their overall rate of treatment. The lack of differences in treatment by race is a positive finding and further highlights the abilities of the integrated healthcare system. The only other recent study that asked a similar research question found differences in treatment by race in the veterans' population. [75] Further, while patients covered by traditional Medicaid programs may be at risk of not receiving immediate treatment, KPMAS is doing better on this metric. We also did not find any differences in persistence to therapy or achievement of sustained virologic response by HIV status. Previous studies have documented the increased risk of HCV-related complications, including liver cancer and chronic kidney disease, with HIV/HCV co-infection [224, 225] and others have demonstrated the benefits of successful HCV for co-infected patients. [226, 227] It is important to ensure that decisions to treat, or not treat, are not based on non-clinical factors that have no bearing on the potential success of treatment. While predictors of treatment may be unique in the KPMAS system, we've seen both clinical and non-clinical factors used in other payer settings as well. [8, 15, 16]

Our study, while limited by time and sample size, is a key first step in understanding the potential for resource offsets with the utilization of the second-generation therapies. Including the timing of treatment allows us to operationalize the changes that occurred in the treatment landscape over the course of our short study period. While Sovaldi, or sofosbuvir, was approved in November of 2013, Harvoni (ledipasvir/sofosbuvir), the most commonly used DAA during our study period, was approved in November of 2014. Using these time indicator variables, we could also determine if there was a difference in utilization when patients are treated earlier versus later – one of the key policy questions being asked in this disease context. Patients treated later, who were found to have increased post-treatment resource use, may have developed more severe disease leading to greater healthcare use. Although the total study period was short, not allowing for a substantial amount of time to pass between the "early" and "late" treatment intervals, the results provide some evidence to support earlier treatment. We did not find a statistically significant effect of treatment in our study, but the direction of the effect is promising.

Our cost-effectiveness analysis is a significant contribution to the literature in the chronic HCV space given the use of key system-specific parameters – rate of sustained virologic response, or the measure of effectiveness

over efficacy, and the initial distribution of the HCV sample across fibrosis scores. The limited applicability of healthcare costs, derived from the literature, to KPMAS, however increased the generalizability of the evaluation of the treatment paradigms. We did aim to provide a societal perspective by including potential loss of income and caregiver costs for patients in the cirrhotic stages of the disease – while most of the current literature focuses on the health system perspective, we take some steps to provide a broader understanding of the optimal strategy.

Although Harvoni was the most commonly used DAA during our study period, from the first two analyses, we used the list price of the most recently approved drug, Mavyret, as the cost of the drug in the base case cost-effectiveness analysis from both perspectives. In this way, we are able to provide KPMAS with recommendations of how to adjust their care pathway, or approach to HCV treatment, once they add this new therapy to their formulary. While understanding how and why health plans place certain drugs on their formularies is a separate research endeavor altogether, by setting the base case price at that of the new drug, we are able to provide KPMAS with actionable evidence in support of a specific policy decision. Given that the new drug, approved in August of 2017, has the lowest list price, is pan-genotypic – approved for all six genotypes of HCV – and has an eight week treatment duration, it may now be the most efficient approach to treating HCV patients. Our study demonstrates, from an economic perspective, why expanded access, with this comparatively lower price, is the optimal treatment strategy.

Finally, given the uncertainty we highlight in the model, the results of our value of information analysis are a major contribution to the literature in this particular area of research. The economic evaluations currently published provide some magnitude of value of these treatment policies from different perspectives – private insurers, CMS, the VA – but do not quantify the amount of investment necessary to improve the confidence in their assessments. We provide estimates of the expected value of perfect information, from both the societal and health care sector perspective, in an effort to value future investments in research to reduce the uncertainty around clinical and potentially economic parameters. For example, if we knew exactly who would be successfully cured or who would require informal caregiver time, we could better, more confidently, identify the optimal treatment strategy.

Future Research

Each of the DAAs on the market is slightly different in its duration, the specific pharmacologic components and the patient population it was approved for – much more work is required to understand all the nuances around using these treatments especially over the long-run. Each patient population – by health system, payer or provider – is unique and understanding treatment patterns in one integrated healthcare system only provides answers from one perspective. For example, substance use, specifically injection drug use, and HCV infection have been linked for a long time. More work, within the KPMAS system and elsewhere, could focus on injection drug users and how they are accessing therapy for HCV. Continued stigma associated with substance use disorders could prevent patients from receiving the treatment they need. Additionally, more work is needed to determine if patients in the older population, those 65 years of age or above, are being appropriately linked to treatment upon diagnosis. Only linking these patients to care in a timely manner will yield the economic and clinical savings demonstrated in this study. [228]

Although the cost-effectiveness literature around this research question continues to grow, pointing towards expanding treatment as the strategy with the most value, payers and health systems, much like KPMAS, can benefit from understanding the immediate, or short-term, effect to their budget. While the long-term savings are well-documented, the fragmented nature of the insurance system in the United States may explain a payer's hesitancy to make the large upfront investment in HCV antivirals. The incentives [229] to pay for these drugs upfront are lacking in our reimbursement approach. Although we did not build an infectious disease model – where we considered how treatment could prevent transmission and therefore limit incidence cases of HCV – including these potential spillover effects would only serve to increase the value of universal access. Formally building this kind of model would provide a true societal, or public health approach, to addressing this disease.

With the approval of the latest pan-genotypic drug, with a list price of $26,500, we might see some of this tension between upfront investment and short-term savings easing. We know that no payer, private or public, pays the list price for a prescription drug. [230] With this 70% reduction from the other most commonly used therapy, Harvoni, policymakers are hopeful payers can expand access to care for their beneficiaries. Further, since the drug has been approved for all genotypes of HCV, essentially covering all cases of HCV previously treated by a variety of other DAAs, it is the hope that this significantly reduced price can drive the competition amongst other antivirals. This new drug was only approved in August of 2017 and so it will take some time until there is widespread use. A

study that measured the composition of the antiviral market over time, with the approval of this new drug, would provide, at least, a general idea of the trends in utilization of antivirals and at a most show the effects of any competition induced by this substantially discounted drug.

Further research should explore these questions in the Medicare population. Simulation models have shown possible effects on the federal payer's budget [231], but determining who is being treated and the effects of these decisions for Medicare beneficiaries can help elucidate not only whether Medicare is facing any barriers to coverage, but if private payers are treating patients at the appropriate time. If patients who recently reached Medicare eligibility are entering this public coverage with advanced cirrhosis, decompensated cirrhosis or liver cancer they may not have had coverage that adequately covered the necessary antivirals. This work could provide a measure of the access issue in the commercial, or employer-sponsored, insurance market. Again, private plans are easing these restrictions [70] but if patients beginning Medicare coverage have advanced liver disease there must be some magnitude of barriers to access.

One limitation of our study was the short follow-up time available to observe patients after treatment completion. Any complications or manifestations of the disease leading to resource utilization, of any magnitude, may not disappear immediately upon cure. Researchers can take advantage of the extensive longitudinal data that can result from following those patients treated today into the future. We aim to update the utilization data for the patients in our study sample. Specifically, we will pull information on healthcare encounters, from the KPMAS database, for about 18 additional months in order to continue observing resource utilization until the end of 2017. By following patients for a longer period of time, we may find other complications due to HCV may resolve and resource use may continue to decrease more significantly. Clinicians will need longer follow-up to determine both long-term adverse effects and benefits of these antivirals.

DAAs in the Context of National Health Policy

The DAA market evolved rapidly over the past few years. As discussed above, Mavyret, Abbvie's latest DAA approved in late 2017, is the first treatment of eight weeks duration approved for all HCV genotypes who have not been previously treated. [232] The manufacturer has initially priced the therapy at about $26,500 for a full course of treatment – a 70% decrease in the list price from Gilead's Harvoni, the current leader in the market. In this particular

sector of the economy, given the way patents are structured for pharmaceutical manufacturers, it is unclear how the entrance of this new product onto the antiviral market could impact the prices of currently used DAAs and the subsequent effect on access to treatment for patients. Basic principles of economics suggest that this new market entrant, at such a discounted price, would induce greater competition amongst those manufacturers with products currently on the market. Gilead, for example, would be forced to drop their price in response to Abbvie's strategic marketing move to set a much lower list price. How manufacturers and payers will negotiate the new market composition will be critical in making these therapies more accessible to patients. In the face of risk-sharing agreements, or outcomes-based reimbursement models, payers can leverage the multiple drug options to make coverage of these therapies more affordable.

During a time when there is so much uncertainty about the current and future state of the healthcare system, the price tags of these cures have shifted the focus of stakeholders in the market to the notion of value in healthcare. Providers, payers, health systems and policymakers are all trying to understand how to define the value of these innovative pharmaceutical products and from whose perspective to determine or assign value to these therapies. The coverage restrictions placed on the new DAAs are a perfect example of how payers, both private and public, inadvertently assign a value to these therapies as a result of which the patient ultimately pays the price.

The value of medicines, in addition to the clinical benefits offered to the patient, is often defined in future terms. Specifically, researchers often assign value to prescription drugs by either 1) future cost and resource savings after treatment or 2) a dollar-per-life-year metric from a cost-effectiveness analysis. This body of work addressed value using both these measures. The cost-effectiveness literature on the new DAAs is quickly growing – providing model simulation results for different patient populations and payer perspectives. While these parameters may vary, each model has and continues to find that expanded access to these drugs, or universal treatment, is cost-effective and even cost-saving in the long-term. [94, 95, 100, 101, 106, 116, 117, 192] However, given the structure of the insurance system in the United States, the incentives to pay for the drugs today in order to accrue savings years into the future are limited. Policy approaches to reduce prescription drug spending such as reference pricing or value-based insurance design could be steps to limit the strain of the immediate investments in covering prescriptions on payer budgets. Even less incentivizing to private payers, with the presence of the disease in the baby-boomer population, is the possibility that after treatment, patients may age into Medicare eligibility in which case the federal payer would

benefit from covering cured patients. [109, 229] One 2015 report, put together by Milliman, Inc. on behalf of Abbvie, shows that aggressively treating Medicare patients with the new DAAs would increase survivorship of beneficiaries and substantially lower costs. Specifically, about 53,000 more people would be alive at the end of 2025 and per-member costs would be about $40,000 lower yielding savings of nearly $3.9 billion over ten years. [231] Benefits like these to the public payer that currently cannot negotiate drug prices are substantial.

The new antiviral therapies have infused a new surge of energy into the pharmaceutical policy debate around manufacturer pricing practices. While the issue of high drug prices and their impact on patients is not new, the pricing of Gilead's Sovaldi sparked a growth in the literature studying drug pricing patterns in the United Sates and possible policy approaches to reducing branded prescription drug prices. Some have focused on legal aspects of the issue [233, 234], while others have focused on the economics. [219]

One major economic issue that has been brought to the forefront of the discussion is the tradeoffs between manufacturer investment in research & development, or innovation, and drug price regulation. While manufacturers are profit-maximizing firms, much like in any other sector of the economy, they often cite the large upfront cost of research as the justification for the high drug prices they set on their products. Proponents of price regulation suggest that by imposing some sort of direct, or indirect, ceiling on initial prices, access to drugs may improve due to reduced prices. Opponents of price regulation warn of the adverse long-term effects – regulating prices may diminish the incentives manufacturers have to make the investments to develop new and improved products. [235-238] Many variations of indirect price regulation, like reference pricing, have been implemented internationally that do not directly place a cap on prices but prevent manufacturers from pricing their drugs significantly different from similar products already on the market. [239-241] A recent report published on affordability of prescription drugs, from the National Academies of Sciences, Engineering and Medicine, summarizes the tension clearly: "drugs that are not affordable are of little value, and drugs that do not exist are of no value." [215]

Other healthcare leaders have provided a public health perspective identifying the unaffordable nature of the DAAs as a threat to the hepatitis C epidemic in the United States. [242] A committee of the National Academy of Medicine has provided the following objective: "the virtual eradication of viral transmission in the United States." Sharfstein et al. highlight the problem with chronic HCV – if manufacturers priced their products at affordable prices, the rest of the stakeholders involved in treatment can focus on screening patients and efficiently connecting

patients to care. [242] However, drug manufacturers have chosen to price their products in such a way that only a fraction of the infected population can access therapy – leaving the health care system "unable to meet the public health need" [242] leading to measures such as coverage restrictions that disproportionately affect those who may need continued support. This is the more pressing issue – pricing a cure for a previously untreatable disease out of the realm of affordability. Further, given this is an infectious disease, the value of treating one patient surpasses the cure of the virus to just that one patient.

We cannot discuss the public health epidemic of Hepatitis C in the United States without addressing the prison population in which the burden of HCV is much greater than the general population - especially since more than half of the current inmates have injected drugs. [243, 244] The Federal Bureau of Prisons' Clinical Practice guidelines, adopted in April 2016, recommend the use of DAAs to treat Hepatitis C in most cases. However, the prices hinder implementation of these recommendations in state prison systems. A recent study surveyed directors of each state department of corrections about HCV treatment practices as of January 2015. [245] Forty-nine directors responded representing 1,348,716 inmates – 106,266 inmates had an HCV infection. Only 949, or 0.89%, of these diagnosed patients were receiving any treatment as of the beginning of 2015. Similar to the initial state Medicaid response to the high prices of Sovaldi [63], the state prison systems used different clinical and non-clinical factors to prioritize treatment for inmates with the infection. [245] The researchers found that the cost of purchasing a twelve-week course of either Harvoni (ledipasvir/sofosbuvir) or Sovaldi (sofosbuvir) varied across states with the prices ranging from $44,421 to $94,500. [245] The cost of treating the more than 100,000 infected patients in these state prison systems puts an incredible strain on department of corrections budgets. This underscores the broader issue of drug pricing practices and policy in the United States. Government entities do receive discounts on the list price when purchasing these drugs, however some state prison systems are spending over 20% of their pharmacy budget on DAAs. Without further financial relief, price will continue to serve as a barrier to treating this vulnerable population. The care setting and resources available to our study sample, at KPMAS, are different than those for incarcerated persons, but an understanding of all patient populations is critical to tackling this public health issue from a national perspective.

Concluding Remarks

The motivating issue behind this body of research is the prohibitive pricing of a cure for an infectious disease of which increasing incidence has created a public health crisis. [242] The antivirals are continually referenced, as a prime example, in the struggle over how to reconcile the many stakeholder perspectives involved in drug pricing policy.

However, the tensions between price and access do not stop at HCV – prices of both new and old pharmaceutical products continue to make the headlines. In December of 2017, Spark Therapeutics received FDA approval for the first gene therapy in the U.S to treat an inherited form of blindness - they priced the treatment, consisting of a single injection in each eye, at $850,000. [246] To some, this is categorically unacceptable, and to those with the condition, this might be what they are willing to pay to reverse their condition. At the same time, we saw the price of Humira, the 'best selling prescription drug in the world," increase 100% over the past five years from $19,000 a year to $38,000 a year. [247] While this drug does not reverse blindness, it is life-changing.

Ensuring manufacturer profits as well as incentives to innovate, while providing timely and appropriate access to necessary medicines is a multifaceted issue with dynamic policy solutions. While there are many moving parts to this issue, understanding the implications of current treatment policies is an important step in developing future solutions to the larger policy issues in this health system. This work is part of the effort to achieve that goal.

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Appendix

Table A1: Negative Binomial Regression – Longitudinal Random Effects Model Results from Panel Data Analysis (All & Ambulatory Encounters) (N=1347)

	All Encounters					Ambulatory Encounters				
Interval	IRR	Std. Err.	P>|z|	95%	CI	IRR	Std. Err.	P>|z|	95%	CI
Tx	0.9099013	0.0762426	0.059	0.7604658	1.0593368	0.8871257	0.074879	0.067	0.74036286	1.03388854
Tx Interval 1	0.9211221	0.1764607	0.668	0.6327779	1.340859	0.8757485	0.1620533	0.473	0.6093523	1.258608
Tx Interval 2	1.188336	0.116404	0.078	0.9807523	1.439856	1.168381	0.1102254	0.099	0.97114	1.405682
Tx Interval 3	1.075028	0.052828	0.141	0.9763167	1.183719	1.106127	0.0525714	0.034	1.007742	1.214116
Tx Interval 4	1.019662	0.0440521	0.652	0.9368763	1.109764	1.040161	0.0434608	0.346	0.9583742	1.128928
Age	0.999542	0.0018527	0.805	0.9959173	1.00318	1.000336	0.00196	0.864	0.996502	1.004185
Gender	0.9862693	0.0290095	0.638	0.9310197	1.044798	0.9965488	0.0311053	0.912	0.9374109	1.059417
Service Area (BALT)										
DCSM	1.113543	0.044972	0.008	1.028797	1.205269	1.10223	0.0432413	0.013	1.020655	1.190325
NOVA	0.9720236	0.1160244	0.812	0.769262	1.228229	0.9407595	0.1041368	0.581	0.7572781	1.168697
Network	1.118539	0.3165061	0.692	0.64238	1.947647	1.144092	0.3228608	0.633	0.6580415	1.989154
State (DC)										
MD	1.019175	0.040351	0.631	0.9430792	1.101411	0.9810895	0.0377313	0.62	0.9098558	1.0579
VA	1.092337	0.1304287	0.459	0.864411	1.380362	1.058175	0.1128488	0.596	0.8585815	1.304169
Race (API)										
Black	1.061785	0.0744986	0.393	0.9253656	1.218316	1.058908	0.0719252	0.399	0.9269176	1.209693
Hisp	1.157525	0.1319867	0.2	0.9257045	1.4474	1.17632	0.1298374	0.141	0.9474869	1.460419
White	1.095624	0.0837471	0.232	0.943186	1.272698	1.130186	0.0790065	0.08	0.9854765	1.296146
Tx History	0.9945844	0.0375205	0.886	0.9236984	1.07091	1.018935	0.0416084	0.646	0.9405619	1.103838
Insurance (Commercial)										
Medicare	1.105144	0.0400685	0.006	1.029336	1.186534	1.097488	0.0367331	0.005	1.027803	1.171898
Medicaid	0.9264542	0.1041977	0.497	0.743173	1.154936	0.9368882	0.1022336	0.55	0.7564921	1.160302
Others	0.9822539	0.1983905	0.929	0.6611538	1.459301	0.9700007	0.1875325	0.875	0.6640599	1.416892
Dual	1.388641	0.4291955	0.288	0.7577121	2.54493	1.373335	0.4030912	0.28	0.7725706	2.441265
Baseline F	1.005271	0.0193312	0.785	0.968088	1.043883	0.9946204	0.0178522	0.764	0.960239	1.030233
Baseline Comorbid Category										
1-2	1.017751	0.034356	0.602	0.9525935	1.087365	0.9985922	0.0326557	0.966	0.9365962	1.064692
3+	1.116617	0.057808	0.033	1.008874	1.235867	1.118925	0.0559729	0.025	1.014426	1.234188
Baseline Liver Complications	0.9860134	0.0428707	0.746	0.9054689	1.073723	0.999701	0.0421678	0.994	0.9203777	1.085861
SUD	1.009012	0.0314734	0.774	0.9491733	1.072623	1.003488	0.0303041	0.908	0.945817	1.064676
Genotype										
2	0.9582112	0.0566646	0.47	0.8533452	1.075964	1.017575	0.0638254	0.781	0.899863	1.150684
3	0.8602292	0.0717202	0.071	0.730544	1.012935	0.8918125	0.0676935	0.131	0.7685332	1.034867
4	0.8726403	0.0972119	0.221	0.701474	1.085573	0.9259668	0.0969295	0.462	0.75421	1.136838
6	0.8296404	0.1377792	0.261	0.5991423	1.148814	0.828673	0.1332592	0.243	0.604646	1.135704
Baseline HBV	1.239709	0.1525776	0.081	0.9739972	1.577908	1.216442	0.1433517	0.096	0.9655645	1.532503
Baseline HIV	0.9664917	0.0575142	0.567	0.8600915	1.086055	0.9854548	0.0568315	0.799	0.8801316	1.103382
Baseline Use	0.9963607	0.0010197	0	0.9943641	0.9983613	0.9993859	0.0010726	0.567	0.9972857	1.00149
_cons	0.6385683	0.1033399	0.006	0.4650042	0.8769157	0.8310688	0.130623	0.239	0.6107305	1.1309
/ln_r	0.8559698	0.0528971		0.7522933	0.9596462	1.382835	0.0661535		1.253177	1.512493
/ln_s	2.897718	0.0718026		2.756988	3.038449	3.004537	0.084709		2.83851	3.170564
r	2.353656	0.1245017		2.12186	2.610773	3.986187	0.2637		3.501448	4.538032
s	18.13272	1.301977		15.75232	20.87284	20.17687	1.709163		17.09029	23.82091
	LR test vs. pooled: chibar2(01) = 1390.31 Prob>=chibar2 = 0.000					LR test vs. pooled: chibar2(01) = 546.89 Prob>=chibar2 = 0.000				

Table A2: Negative Binomial Regression – Longitudinal Random Effects Model Results from Panel Data Analysis (Emergency Department & Inpatient Encounters) (N=1347)

	Emergency Department Encounters					Inpatient Encounters				
Interval	IRR	Std. Err.	P>|z|	95%	CI	IRR	Std. Err.	P>|z|	95%	CI
Tx	0.7057071	0.1770849	0.145	0.3586207	1.0527935	0.8110677	0.1098042	0.073	0.59585147	1.02628393
Tx Interval 1	0.9302715	0.5983359	0.911	0.2637122	3.281626	0.326391	0.3502622	0.297	0.0398366	2.6742
Tx Interval 2	1.038187	0.3161231	0.902	0.5715958	1.885656	1.157292	0.407677	0.678	0.5802188	2.30831
Tx Interval 3	1.410084	0.177261	0.006	1.102151	1.804053	1.188061	0.1885846	0.278	0.870412	1.621633
Tx Interval 4	1.181858	0.1326543	0.137	0.9484719	1.472672	1.177214	0.1657985	0.247	0.8932486	1.551452
Age	1.007635	0.0059909	0.201	0.9959616	1.019446	0.9976717	0.007907	0.756	0.9830977	1.012462
Gender	1.127456	0.0899302	0.133	0.9642828	1.31824	0.9730859	0.0943525	0.778	0.8046683	1.176753
Service Area (BALT)										
DCSM	0.8973748	0.1028919	0.345	0.7167639	1.123496	1.070508	0.1420583	0.608	0.8253419	1.3885
NOVA	0.7659465	0.2276273	0.37	0.427794	1.371394	0.9842783	0.4230986	0.971	0.4238609	2.285665
Network State(DC)	4.32E-08	0.0001384	0.996	0	.	1.07E-07	0.0002837	0.995	0	.
MD	0.9567634	0.1003654	0.674	0.7789556	1.175158	1.052915	0.1380383	0.694	0.8143292	1.361403
VA	1.128893	0.3306502	0.679	0.6358252	2.004323	1.043459	0.4393251	0.92	0.4571896	2.381523
Race (API)										
Black	0.7583066	0.1338078	0.117	0.5365933	1.071629	0.9825194	0.2528938	0.945	0.5932636	1.627176
Hisp	0.8524507	0.275329	0.621	0.4526304	1.605443	1.028322	0.4010434	0.943	0.4788086	2.208492
White	0.8434981	0.1533004	0.349	0.5907226	1.204438	0.9871543	0.2616123	0.961	0.5872222	1.659463
Tx History	1.086175	0.1115319	0.421	0.8881694	1.328324	0.900999	0.1119694	0.402	0.7062254	1.14949
Insurance (Commercial)										
Medicare	0.9363722	0.0878801	0.484	0.7790437	1.125473	1.010595	0.1181051	0.928	0.8037108	1.270733
Medicaid	0.9384103	0.2863404	0.835	0.5160154	1.706565	0.6603708	0.2743718	0.318	0.2925024	1.490892
Other	0.3964394	0.3010356	0.223	0.0894991	1.756043	1.461948	0.9566241	0.562	0.4054609	5.271264
Duals	0.6949174	0.7960248	0.751	0.0736013	6.561162	1.587975	1.504782	0.626	0.2478765	10.17306
Baseline F	0.9230332	0.0457636	0.106	0.8375584	1.017231	1.001639	0.0614758	0.979	0.8881137	1.129676
Baseline Comorbid Category (0)										
1-2	1.107613	0.1009915	0.262	0.9263513	1.324341	1.003514	0.1121005	0.975	0.8061902	1.249135
3+	0.9781517	0.1400188	0.877	0.7388562	1.294949	0.9420991	0.1637264	0.731	0.6701425	1.324421
Baseline Liver Complications	0.9097652	0.1188413	0.469	0.5748633	1.2031	0.8792029	0.1312041	0.388	0.6562415	1.177917
Baseline SUD	0.9609316	0.0803274	0.634	0.8157138	1.132002	0.9435593	0.0979017	0.576	0.7699284	1.156347
Genotype										
2	0.8357199	0.1404017	0.285	0.6012542	1.161618	0.9280013	0.1832041	0.705	0.6302403	1.366441
3	1.12075	0.2295558	0.578	0.7501753	1.674383	1.339509	0.322852	0.225	0.8351931	2.148347
4	0.9061352	0.2835782	0.753	0.4906891	1.673322	0.4034109	0.2011541	0.069	0.1518134	1.071976
6	0.8014427	0.3769867	0.638	0.3187719	2.014953	1.0145	0.4718438	0.975	0.4077162	2.524328
Baseline HBV	0.8811423	0.2985321	0.709	0.4535841	1.711726	0.655481	0.3109715	0.373	0.2586637	1.661058
Baseline HIV	1.210735	0.1852515	0.211	0.8970335	1.63414	1.403244	0.2592754	0.067	0.9769179	2.015619
Baseline Use	1.014701	0.0023374	0	1.01013	1.019293	1.011592	0.0024521	0	1.006798	1.01641
_cons	0.1099613	0.0487376	0	0.0461282	0.2621281	0.1197447	0.0663958	0	0.0403909	0.3550003
/ln_r	0.8954781	0.0998044		0.6998652	1.091091	0.393305	0.0820109		0.2325665	0.5540435
/ln_s	0.649117	0.1716111		0.3127654	0.9854686	-0.0742495	0.15985		-0.3875497	0.2390507
r	2.448506	0.2443716		2.013481	2.977521	1.48187	0.1215296		1.261834	1.740276
s	1.91385	0.328438		1.367201	2.679067	0.92844	0.1484111		0.6787179	1.270043
	LR test vs. pooled: chibar2(01) = 109.65 Prob>=chibar2 = 0.000					LR test vs. pooled: chibar2(01) = 223.76 Prob>=chibar2 = 0.000				

Table A3: Negative Binomial Regression – Longitudinal, Population Averaged Model with Autoregressive Order 1 Correlation Structure (All & Ambulatory Encounters) (N=1347)

	All Encounters					Ambulatory Encounters				
Interval	IRR	Std. Err.	P>|z|	95%	CI	IRR	Std. Err.	P>|z|	95%	CI
Tx	0.957392	0.0436924	0.34	0.8754747	1.046974	0.9974163	0.0447176	0.954	0.9135118	1.089027
Tx Interval 1	0.4410095	0.0869546	0	0.2996506	0.6490539	0.9983939	0.0022579	0.477	0.9939782	1.002829
Tx Interval 2	0.9904567	0.0981012	0.923	0.8156935	1.202663	0.5893382	0.1415241	0.028	0.3680921	0.943567
Tx Interval 3	1.068982	0.0526052	0.175	0.9706939	1.177222	1.150594	0.1378454	0.242	0.9097977	1.455121
Tx Interval 4	1.134926	0.0486354	0.003	1.043496	1.234368	1.041663	0.0612404	0.487	0.9282913	1.168881
Age	0.9984754	0.0018132	0.401	0.9949279	1.002035	1.05998	0.055586	0.267	0.9564457	1.174723
Gender	0.992771	0.0284734	0.8	0.9385037	1.050176	0.9417318	0.0336223	0.093	0.8780861	1.009991
Service Area (BALT)										
DCSM	1.013048	0.0400266	0.743	0.9375579	1.094616	1.115479	0.0549924	0.027	1.012739	1.228641
NOVA	0.9612706	0.1038046	0.715	0.7779058	1.187857	1.04026	0.1396048	0.769	0.7996671	1.35324
Network	0.5302821	0.1713464	0.05	0.2814908	0.9989639	0.8672126	0.3400168	0.716	0.4021485	1.8701
State (DC)										
MD	0.8859774	0.0342546	0.002	0.8213203	0.9557245	1.021298	0.0493247	0.663	0.9290582	1.122696
VA	0.883502	0.0946552	0.248	0.7161646	1.089939	1.002581	0.1334903	0.985	0.772298	1.30153
Race (API)										
Black	1.022082	0.0688916	0.746	0.8955956	1.166432	1.009557	0.0845197	0.91	0.8567784	1.189578
Hisp	1.086738	0.1208754	0.455	0.8738712	1.351456	1.029555	0.1426161	0.833	0.7847644	1.350703
White	1.111633	0.0772023	0.128	0.9701659	1.273729	1.009189	0.0871061	0.916	0.8521239	1.195204
Tx History	1.05296	0.0386392	0.16	0.9798881	1.131482	1.017223	0.0464341	0.708	0.9301667	1.112428
Insurance (Commercial)										
Medicare	1.071586	0.0364068	0.042	1.002554	1.145371	1.050481	0.0444627	0.245	0.9668526	1.141343
Medicaid	0.8094813	0.0890735	0.055	0.6524429	1.004318	0.8725081	0.1190322	0.317	0.6677964	1.139974
Other	1.071402	0.2042472	0.718	0.7373658	1.556759	0.8946495	0.2159102	0.645	0.5574787	1.435746
Dual	0.7023136	0.221207	0.262	0.3788166	1.302066	0.830626	0.3233483	0.634	0.3873	1.781408
Baseline F	1.019475	0.018414	0.286	0.9840159	1.056213	1.017886	0.0229069	0.431	0.9739654	1.063788
Baseline comorbid Category										
1-2	0.8890386	0.0691914	0.065	0.75342346	1.024653744	0.99281	0.0407137	0.86	0.9161353	1.075902
3+	0.9472782	0.0482488	0.288	0.8572792	1.046725	1.088273	0.0689911	0.182	0.9611158	1.232252
Baseline Liver Complications	1.036161	0.0441178	0.404	0.9532011	1.12634	0.9735885	0.0517406	0.615	0.8772815	1.080468
SUD	0.9797661	0.0298713	0.503	0.9229344	1.040097	1.011251	0.0384035	0.768	0.9387146	1.089393
Genotype										
2	0.9529542	0.0544664	0.399	0.8519642	1.065915	0.9983267	0.0708614	0.981	0.8686688	1.147337
3	0.9629321	0.0727783	0.617	0.8303514	1.116682	0.926523	0.0876603	0.42	0.7697013	1.115296
4	0.6572836	0.070833	0	0.5321352	0.8118646	0.8615664	0.114415	0.262	0.6641255	1.117705
6	0.7778701	0.1235394	0.114	0.5697986	1.061922	0.955475	0.1873801	0.816	0.6505617	1.403299
Baseline HBV	0.9822116	0.1198264	0.883	0.7733239	1.247523	1.033018	0.1554588	0.829	0.7691491	1.387411
Baseline HIV	0.982249	0.0574069	0.759	0.8759385	1.101462	0.927292	0.0676853	0.301	0.8036839	1.069911
Baseline Use	1.026404	0.0010095	0	1.024427	1.028384	1.028386	0.0012451	0	1.025948	1.030829
_cons	6.681414	1.045008	0	4.917405	9.078222	4.252233	0.8278321	0	2.903379	6.22774

Table A4: Negative Binomial Regression – Longitudinal, Population Averaged Model with Autoregressive Order 1 Correlation Structure (Emergency Department and Inpatient Encounters) (N=1347)

	Emergency Department					Inpatient				
Interval	IRR	Std. Err.	P>|z|	0.95	CI	IRR	Std. Err.	P>|z|	95%	CI
Tx	0.8224852	0.1141257	0.11	0.59879883	1.046171572	0.794014	0.113864	0.076	0.57084056	1.01718744
Tx Interval 1	1.00421	0.0042955	0.326	0.9958257	1.012664	0.1239835	0.134234	0.054	0.0148521	1.034998
Tx Interval 2	0.5510331	0.3462506	0.343	0.1608093	1.888183	0.4756907	0.1493086	0.018	0.2571294	0.8800303
Tx Interval 3	0.6758105	0.1926109	0.169	0.3865683	1.181472	1.200989	0.1248159	0.078	0.9796612	1.472321
Tx Interval 4	1.354756	0.1398826	0.003	1.106553	1.658633	1.279465	0.114403	0.006	1.073788	1.524538
Age	1.263408	0.1158872	0.011	1.055519	1.51224	0.995047	0.0040572	0.223	0.9871267	1.003031
Gender	1.128787	0.1183714	0.085	0.89677906	1.360794944	1.109016	0.0742638	0.075	0.96345895	1.254573048
Service Area (BALT)										
DCSM	0.8403513	0.0723961	0.043	0.7097902	0.9949283	0.8067607	0.0697751	0.013	0.680967	0.9557921
NOVA	0.9004723	0.2216151	0.67	0.5558803	1.458678	0.8976959	0.2096606	0.644	0.5679729	1.418832
Network State(DC)	2.06E-09	0.000027	0.999	0	.	2.06E-09	0.0000267	0.999	0	.
MD	0.8460227	0.0717691	0.049	0.7164297	0.9990573	0.5684401	0.0451027	0	0.4865712	0.6640841
VA	0.6889931	0.1687808	0.128	0.4262833	1.113606	0.835915	0.1232244	0.076	0.59439518	1.077434824
Race (API)										
Black	0.8322218	0.1219298	0.21	0.6244944	1.109046	1.19831	0.2041167	0.288	0.8581793	1.673249
Hisp	0.9229576	0.2205952	0.737	0.577746	1.474438	1.455949	0.3606515	0.129	0.8959751	2.3659
White	0.8498622	0.1284988	0.282	0.6318983	1.143009	1.328688	0.2477706	0.089	0.84305762	1.814318376
Tx History	0.9818735	0.081688	0.826	0.83414	1.155772	1.143036	0.1086742	0.072	0.93003457	1.356037432
Insurance (Commercial)										
Medicare	0.9650179	0.0743268	0.644	0.8298027	1.122266	1.137687	0.0858906	0.088	0.9812067	1.319122
Medicaid	0.8306252	0.2253476	0.494	0.4880622	1.413628	0.6557381	0.2052299	0.178	0.3550793	1.210976
Other	0.5341886	0.305922	0.274	0.1738697	1.641214	1.356262	0.5370922	0.442	0.6241084	2.94732
Duals	0.2532538	0.2988911	0.245	0.025059	2.559454	0.6035846	0.5185847	0.557	0.1120488	3.25139
Baseline F	0.9350042	0.0382935	0.101	0.8628836	1.013153	1.069935	0.0426479	0.09	0.9895282	1.156875
Baseline Comorbid Category (0)										
1-2	1.015009	0.0749397	0.84	0.8782623	1.173047	0.8612317	0.0907862	0.089	0.68329075	1.039172652
3+	0.9118314	0.1080642	0.436	0.7228294	1.150253	0.8266995	0.1108906	0.084	0.60935392	1.044045076
Baseline Liver Complications	1.013956	0.0982825	0.886	0.8385177	1.2261	1.16204	0.1076177	0.105	0.9691485	1.393322
Baseline SUD	0.8745998	0.0606133	0.053	0.7635151	1.001846	0.8567712	0.0958393	0.065	0.66892617	1.044616228
Genotype										
2	0.6645488	0.1026801	0.008	0.4909156	0.8995948	0.9826869	0.1305971	0.895	0.7573423	1.275082
3	1.141583	0.1943378	0.437	0.8177168	1.59372	1.093294	0.1830888	0.594	0.7873903	1.518041
4	0.5675276	0.1749852	0.066	0.3101251	1.038573	0.2794598	0.1165277	0.002	0.1234212	0.6327744
6	0.6584379	0.2775913	0.322	0.288175	1.504435	0.4793069	0.1862535	0.058	0.2237927	1.026553
Baseline HBV	1.279349	0.3234852	0.33	0.7794018	2.099986	0.4828564	0.1844067	0.057	0.2284217	1.020701
Baseline HIV	1.104257	0.1081691	0.091	0.89224556	1.316268436	1.170182	0.1516233	0.225	0.9077392	1.508501
Baseline Use	1.022043	0.0017246	0	1.018669	1.025429	1.029518	0.0015876	0	1.026411	1.032635
_cons	0.1831615	0.0657094	0	0.0906703	0.3700016	0.1421129	0.0517025	0	0.0696555	0.2899421

Table A5: CEA Model Parameters

Parameter Name	Description of Parameter	Base Case	Low	High	Distribution	Reference
pF0	Incidence of stage F0	0.05	0.004	0.204	Dirichlet (LIST	KPMAS Study Sample (n=105); refers to # of patients with this F-score in analysis from Aim 1
pF1	Incidence of stage F1	0.25	0.1	0.46	Dirichlet (LIST	KPMAS Study Sample (n=572); refers to # of patients with this F-score in analysis from Aim 1
pF2	Incidence of stage F2	0.41	0.22	0.6	Dirichlet (LIST	KPMAS Study Sample (n=933); refers to # of patients with this F-score in analysis from Aim 1
pF3	Incidence of stage F3	0.25	0.1	0.41	Dirichlet (LIST	KPMAS Study Sample (n=533); refers to # of patients with this F-score in analysis from Aim 1
pF4	Incidence of stage F4	0.04	0.001	0.141	Dirichlet (LIST	KPMAS Study Sample (n=85); refers to # of patients with this F-score in analysis from Aim 1
pDCC	Incidence of decompensated cirrhosis	0	-	-		All patients begin in F0-F4 and so initial probability in the Markov movel is 0
pHCC	Incidence of hepatocellular carcinoma	0	-	-		All patients begin in F0-F4 and so initial probability in the Markov movel is 0
pLT	Incidence of Liver transplant	0	-	-		All patients begin in F0-F4 and so initial probability in the Markov movel is 0
pDeath	Initial probability of death	0	-	-		All patients begin in F0-F4 and so initial probability in the Markov movel is 0
pF0_SVR	Incidence of cure after F0	0	-	-		All patients begin in F0-F4 and so initial probability in the Markov movel is 0
pF1_SVR	Incidence of cure after F1	0	-	-		All patients begin in F0-F4 and so initial probability in the Markov movel is 0
pF2_SVR	Incidence of cure after F2	0	-	-		All patients begin in F0-F4 and so initial probability in the Markov movel is 0
pF3_SVR	Incidence of cure after F3	0	-	-		All patients begin in F0-F4 and so initial probability in the Markov movel is 0
pF4_SVR	Incidence of cure after F4	0	-	-		All patients begin in F0-F4 and so initial probability in the Markov movel is 0
pDCC_SVR	Incidence of cure after DCC	0	-	-		All patients begin in F0-F4 and so initial probability in the Markov movel is 0
pHCC_SVR	Incidence of cure after HCC	0	-	-		All patients begin in F0-F4 and so initial probability in the Markov movel is 0
pLT_SVR	Incidence of cure after LT	0	-	-		All patients begin in F0-F4 and so initial probability in the Markov movel is 0

Table A5: CEA Model Parameters (cont.)

Parameter Name	Description of Parameter	Base Case	Low	High	Distribution	Reference	Alpha	Beta
pF0toF1	Transition probability from F0 to F1	0.117	0.104	0.13	Beta (Mean = 0.116998826; SE = 0.00662856)	Chhatwal, J., et al. "Cost-Effectiveness and Budget Impact of Hepatitis C Virus Treatment with Sofosbuvir and Ledipasvir in the United States." Ann Intern Med 162.6 (2015): 397-406. Print.; Thein H-H, Yi Q, Dore GJ, Krahn MD. Estimation of stage-specific fibrosis progression rates in chronic hepatitis C virus infection: a meta-analysis and meta-regression. Hepatology. 2008;48(2):418-431.	274.98	2075.3
pF0toDeath	Probability of death from F0	0.008237				https://www.cdc.gov/nchs/fastats/deaths.htm		
pF1_postSVR	Transition probability from F0 to F1 after cure	0.01053	0.0078975	0.0131625	Uniform : +/- 25%	Assumption - pF0toF1 * .09		
pF1postF0_TxFail	Transition probability from F0 to F1 after Tx failure	0.117	0.104	0.13	Beta (Mean = 0.116998826; SE = 0.00662856)	Chhatwal, J., et al. "Cost-Effectiveness and Budget Impact of Hepatitis C Virus Treatment with Sofosbuvir and Ledipasvir in the United States." Ann Intern Med 162.6 (2015): 397-406. Print.; Thein H-H, Yi Q, Dore GJ, Krahn MD. Estimation of stage-specific fibrosis progression rates in chronic hepatitis C virus infection: a meta-analysis and meta-regression. Hepatology. 2008;48(2):418-431.	274.98	2075.3
pDeath_F0TxFail	Probability of Death from F0 after Tx Failure	0.008237				https://www.cdc.gov/nchs/fastats/deaths.htm		
pF1toF2	Transition probability from F1 to F2	0.085	0.075	0.096	Beta (Mean = 0.085001861; SE = 0.005608917)	Thein H-H, Yi Q, Dore GJ, Krahn MD. Estimation of stage-specific fibrosis progression rates in chronic hepatitis C virus infection: a meta-analysis and meta-regression. Hepatology. 2008;48(2):418-431.(Chhatwaletal 2015, Aggarwaletal2017, Chanetal 2013, Chhatwal 2017)	210.06	2261.18
pF1toDeath	Probability of death from F1	0.008237				https://www.cdc.gov/nchs/fastats/deaths.htm		
pF2_postSVR	Transition probability from F1 to F2 after cure	0.00765	0.0057375	0.0095625	Uniform (+/- 25%)	Assumption - pF1toF2 * .09		
pF2postF1_TxFail	Transition probability from F1 to F2 after Tx failure	0.085	0.075	0.096	Beta (Mean = 0.085001861; SE = 0.005608917)	Thein H-H, Yi Q, Dore GJ, Krahn MD. Estimation of stage-specific fibrosis progression rates in chronic hepatitis C virus infection: a meta-analysis and meta-regression. Hepatology. 2008;48(2):418-431.(Chhatwaletal 2015, Aggarwaletal2017, Chanetal 2013, Chhatwal 2017)	210.06	2261.18
pDeath_F1TxFail	Probability of death from F1 after Tx failure	0.008237				https://www.cdc.gov/nchs/fastats/deaths.htm		
pF2toF3	Transition probabiliy from F2 to F3	0.12	0.109	0.133	Beta (Mean = 0.119999333; SE = 0.006631258)	Thein H-H, Yi Q, Dore GJ, Krahn MD. Estimation of stage-specific fibrosis progression rates in chronic hepatitis C virus infection: a meta-analysis and meta-regression. Hepatology. 2008;48(2):418-431.	288.05	2112.38
pF2toDeath	Probability of death from F2	0.008237				https://www.cdc.gov/nchs/fastats/deaths.htm		
pF3_postSVR	Transition probability from F2 to F3 after cure	0.0108	0.0081	0.0135	Uniform (+/- 25%)	Assumption - pF2toF3 * .09		
pF3postF2_TxFail	Transition probability from F2 to F3 after Tx failure	0.12	0.109	0.133	Beta (Mean = 0.119999333; SE = 0.006631258)	Thein H-H, Yi Q, Dore GJ, Krahn MD. Estimation of stage-specific fibrosis progression rates in chronic hepatitis C virus infection: a meta-analysis and meta-regression. Hepatology. 2008;48(2):418-431.	288.05	2112.38
pF3toF4	Transition probability from F3 to F4	0.116	0.104	0.129	Beta (Mean = 0.116000737; SE = 0.006628599)	Thein H-H, Yi Q, Dore GJ, Krahn MD. Estimation of stage-specific fibrosis progression rates in chronic hepatitis C virus infection: a meta-analysis and meta-regression. Hepatology. 2008;48(2):418-431.	270.61	2062.22
pDeath_F2TxFail	Probability of death from F2 after Tx failure	0.008237				https://www.cdc.gov/nchs/fastats/deaths.htm		
pF4_postSVR	Transition probability from F3 to F4 after cure	0.01044	0.00783	0.01305	Uniform : +/- 25%	Assumption - pF3toF4 * .09		

Table A5: CEA Model Parameters (cont.)

Parameter Name	Description of Parameter	Base Case	Low	High	Distribution	Reference	Alpha	Beta
pF4postF3_TxFail	Transition probability from F3 to F4 after Tx failure	0.116	0.104	0.129	Beta (Mean = 0.116000737; SE = 0.006628599)	Thein H-H, Yi Q, Dore GJ, Krahn MD. Estimation of stage-specific fibrosis progression rates in chronic hepatitis C virus infection: a meta-analysis and meta-regression. Hepatology. 2008;48(2):418-431.	270.61	2062.22
pDeath_F3TxFail	Probability of Death from F3 after Tx failure	0.008237 * 2.37				https://www.cdc.gov/nchs/fastats/deaths.htm; El-Kamary SS, Jhaveri R, Shardell MD. All-cause, liver-related, and non-liver-related mortality among HCVinfected individuals in the general US population. Clinical infectious diseases : an official publication of the Infectious Diseases Society of America. Jul 15 2011;53(2):150-157.		
pDCC_F4postSVR	Transition probability to DCCfrom F4 after cure	0.001	2.5011E-05	0.00197499	Beta (Mean = 0.000999978; SE = 0.000497443)	Saab S, Hunt DR, Stone MA, McClune A, Tong MJ. Timing of hepatitis C antiviral therapy in patients with advanced liver disease: A decision analysis model. Liver Transplantation. 2010;16(6):748-59.		
pHCC_F4postSVR	Transition probability to HCC from F4 after cure	0.005	0.002	0.013	Beta (Mean = 0.004989619; SE = 0.004070634)	Cardoso AC, Moucari R, Figueiredo-Mendes C, Ripault MP, Giuily N, Castelnau C, et al. Impact of peginterferon and ribavirin therapy on hepatocellular carcinoma: incidence and survival in hepatitis C patients with advanced fibrosis. Journal of Hepatology. 2010;52(5):652-7.	1.49	297.13
pDCCpostF4_TxFail	Transition probability to DCC from F4 after Tx failure transition	0.039	0.01	0.079	Beta (Mean = 0.039004334; SE = 0.020296461)	Fattovich G, Giustina G, Degos F, Tremolada F, Diodati G, Almasio P, et al. Morbidity and mortality in compensated cirrhosis type C: a retrospective follow-up study of 384 patients. Gastroenterology. 1997;112(2):463-72.	3.51	86.48
pHCCpostF4_TxFail	probability to HCC from F4 after Tx failure	0.014	0.01	0.079	Beta (Mean = 0.01433121; SE = 0.032275806)	Fattovich G, Giustina G, Degos F, Tremolada F, Diodati G, Almasio P, et al. Morbidity and mortality in compensated cirrhosis type C: a retrospective follow-up study of 384 patients. Gastroenterology. 1997;112(2):463-72.	0.18	12.38
pDeath_F4TxFail	probability of death from F4 after Tx failure	0.008237 * 2.37				https://www.cdc.gov/nchs/fastats/deaths.htm; El-Kamary SS, Jhaveri R, Shardell MD. All-cause, liver-related, and non-liver-related mortality among HCVinfected individuals in the general US population. Clinical infectious diseases : an official publication of the Infectious Diseases Society of America. Jul 15 2011;53(2):150-157.		
pLT_postSVR	Probability of transition to Liver transplant after cure	0.012	0.007	0.016	Beta (Mean = 0.012738854; SE = 0.030454491)	Razavi H, Elkhoury AC, Elbasha E, et al. Chronic hepatitis C virus (HCV) disease burden and cost in the United States. Hepatology. Jun 2013;57(6):2164-2170.	0.16	12.4
pHCC_DCCpostSVR	Transition probability from DCC to HCC after cure	0.01	0.0075	0.0125	Uniform : +/- 25%	HaganLM,SulkowskiMS,SchinaziRF. Costanalysis of sofosbuvir/ribavirin versus sofosbuvir/simeprevir for genotype1 hepatitisC virus in interferon ineligible/intolerant individuals. Hepatology2014;60:37–45.;		
pLTpostDCC_TxFail	Transition probability from DCC to liver transplant after Tx failure	0.023	0.01	0.062	Beta (Mean = 0.0230837; SE = 0.01976084)	Davis G, Alter M, El-Serag H, Poynard T, Jennings L. Aging of hepatitis C virus (HCV)-infected persons in the United States: a multiple cohort model of HCV prevalence and disease progression. Gastroenterology. 2010;138(2):513-21.; Thuluvath P, Guidinger M, Fung J, Johnson L, Rayhill S, Pelletier S. Liver transplantation in the United States, 1999–2008. American Journal of Transplantation. 2010;10(4p2):1003-19.	1.31	55.44
pDeath_DCCTxFail	Probability of death from DCC after Tx failure	0.182	0.065	0.19	Beta	Planas R, Ballesté B, Antonio Álvarez M, Rivera M, Montoliu S, Anton Galeras J, et al. Natural history of decompensated hepatitis C virus-related cirrhosis. A study of 200 patients. Journal of Hepatology. 2004;40(5):823-30.	1626.4	7309.88
pLTpostHCC_TxFail	probability of transition from HCC to liver transplant after Tx failure	0.04	0	0.14	Beta	Lang K, Danchenko N, Gondek K, Shah S, Thompson D. The burden of illness associated with hepatocellular carcinoma in the United States. Journal of Hepatology. 2009;50(1):89-99.; Saab S, Hunt DR, Stone MA, McClune A, Tong MJ. Timing of hepatitis C antiviral therapy in patients with advanced liver disease: A decision analysis model. Liver Transplantation. 2010;16(6):748-59.	0.59	14.16
pDeath_HCCTxFail	Probability of death from HCC after tx failure	0.427	0.33	0.86	Beta	Fattovich G, Giustina G, Degos F, Tremolada F, Diodati G, Almasio P, et al. Morbidity and mortality in compensated cirrhosis type C: a retrospective follow-up study of 384 patients. Gastroenterology. 1997;112(2):463-72.;	2.14	2.87
pDeath_LTTxFail	Probability of death from liver transplant from Tx failure	0.116	0.06	0.42	Beta	Wolfe R, Roys E, Merion R. Trends in Organ Donation and Transplantation in the United States, 1999–2008. American Journal of Transplantation. 2010;10(4p2):961-72.	1.37	6.88

Table A5: CEA Model Parameters (cont.)

Parameter Name	Description of Parameter	Base Case	Low	High	Distribution	Reference
pF0toSVR (pSVR_fromstates_dist)	probability of cure from F0	0.95	0.85	1	Beta (Mean = 0.925; SE = 0.038265306)	KPMAS; Falade-Nwulia, O., et al. "Oral Direct-Acting Agent Therapy for Hepatitis C Virus Infection: A Systematic Review." Ann Intern Med (2017). Print.
pF1toSVR (pSVR_fromstates_dist)	probability of cure from F1	0.95	0.85	1	Beta (Mean = 0.925; SE = 0.038265306)	KPMAS; Falade-Nwulia, O., et al. "Oral Direct-Acting Agent Therapy for Hepatitis C Virus Infection: A Systematic Review." Ann Intern Med (2017). Print.
pF2toSVR (pSVR_fromstates_dist)	probability of cure from F2	0.95	0.85	1	Beta (Mean = 0.925; SE = 0.038265306)	KPMAS; Falade-Nwulia, O., et al. "Oral Direct-Acting Agent Therapy for Hepatitis C Virus Infection: A Systematic Review." Ann Intern Med (2017). Print.
pF3toSVR (pSVR_fromstates_dist)	probability of cure from F3	0.95	0.85	1	Beta (Mean = 0.925; SE = 0.038265306)	KPMAS; Falade-Nwulia, O., et al. "Oral Direct-Acting Agent Therapy for Hepatitis C Virus Infection: A Systematic Review." Ann Intern Med (2017). Print.
pF4toSVR (pSVR_fromstates_dist)	probability of cure from F4	0.95	0.85	1	Beta (Mean = 0.925; SE = 0.038265306)	KPMAS; Falade-Nwulia, O., et al. "Oral Direct-Acting Agent Therapy for Hepatitis C Virus Infection: A Systematic Review." Ann Intern Med (2017). Print.
pDCCtoSVR (pSVR_fromstates_dist)	probability of cure from DCC	0.95	0.85	1	Beta (Mean = 0.925; SE = 0.038265306)	KPMAS; Falade-Nwulia, O., et al. "Oral Direct-Acting Agent Therapy for Hepatitis C Virus Infection: A Systematic Review." Ann Intern Med (2017). Print.
pHCCtoSVR (pSVR_fromstates_dist)	probability of cure from HCC	0.95	0.85	1	Beta (Mean = 0.925; SE = 0.038265306)	KPMAS; Falade-Nwulia, O., et al. "Oral Direct-Acting Agent Therapy for Hepatitis C Virus Infection: A Systematic Review." Ann Intern Med (2017). Print.
pLTtoSVR (pSVR_fromstates_dist)	probability of cure from liver transplant	0.95	0.85	1	Beta (Mean = 0.925; SE = 0.038265306)	KPMAS; Falade-Nwulia, O., et al. "Oral Direct-Acting Agent Therapy for Hepatitis C Virus Infection: A Systematic Review." Ann Intern Med (2017). Print.

Table A5: CEA Model Parameters (cont.)

Parameter Name	Description of Parameter	Base Case	Min	Max	Distribution	Reference	Alpha	Beta
cost_F0	Annual health state cost for F0 (Adjusted to 2016 $)	775.468881	581.60166	969.336101	Gamma (Mean = 0.324466962; SE = 0.08276249)	Davis KL, Mitra D, Medjedovic J, Beam C, Rustgi V. Direct economic burden of chronic hepatitis C virus in a United States managed care population. Journal of Clinical Gastroenterology. 2011;45(2):e17.; McAdam-Marx C, McGarry LJ, Hane CA, Biskupiak J, Deniz B, Brixner DI. All-cause and incremental per patient per year cost associated with chronic hepatitis C virus and associated liver complications in the United States: A managed care perspective. J Manag Care Pharm. 2011;17(7):531-46.	15.37	47.37
cost_F1	Annual health state cost for F1 (Adjusted to 2016 $)	775.468881	581.60166	969.336101	Gamma (Mean = 0.324466962; SE = 0.08276249)	Davis KL, Mitra D, Medjedovic J, Beam C, Rustgi V. Direct economic burden of chronic hepatitis C virus in a United States managed care population. Journal of Clinical Gastroenterology. 2011;45(2):e17.; McAdam-Marx C, McGarry LJ, Hane CA, Biskupiak J, Deniz B, Brixner DI. All-cause and incremental per patient per year cost associated with chronic hepatitis C virus and associated liver complications in the United States: A managed care perspective. J Manag Care Pharm. 2011;17(7):531-46.	15.37	47.37
cost_F2	Annual health state cost for F2 (Adjusted to 2016 $)	785.055721	588.791791	981.319652	Gamma (Mean = 0.320341809; SE = 0.081710278)	Davis KL, Mitra D, Medjedovic J, Beam C, Rustgi V. Direct economic burden of chronic hepatitis C virus in a United States managed care population. Journal of Clinical Gastroenterology. 2011;45(2):e17.; McAdam-Marx C, McGarry LJ, Hane CA, Biskupiak J, Deniz B, Brixner DI. All-cause and incremental per patient per year cost associated with chronic hepatitis C virus and associated liver complications in the United States: A managed care perspective. J Manag Care Pharm. 2011;17(7):531-46.	15.37	47.98
cost_F3	Annual health state cost for F3 (Adjusted to 2016 $)	1593.54594	1195.15946	1991.93243	Gamma (Mean = 0.157900144; SE = 0.040275931)	Davis KL, Mitra D, Medjedovic J, Beam C, Rustgi V. Direct economic burden of chronic hepatitis C virus in a United States managed care population. Journal of Clinical Gastroenterology. 2011;45(2):e17.; McAdam-Marx C, McGarry LJ, Hane CA, Biskupiak J, Deniz B, Brixner DI. All-cause and incremental per patient per year cost associated with chronic hepatitis C virus and associated liver complications in the United States: A managed care perspective. J Manag Care Pharm. 2011;17(7):531-46.	15.37	97.34
cost_F4	Annual health state cost for F4 (Adjusted to 2016 $)	1858.78186	1394.0864	2323.47733	Gamma (Mean = 0.135311207; SE = 0.034514122)	Davis KL, Mitra D, Medjedovic J, Beam C, Rustgi V. Direct economic burden of chronic hepatitis C virus in a United States managed care population. Journal of Clinical Gastroenterology. 2011;45(2):e17.; McAdam-Marx C, McGarry LJ, Hane CA, Biskupiak J, Deniz B, Brixner DI. All-cause and incremental per patient per year cost associated with chronic hepatitis C virus and associated liver complications in the United States: A managed care perspective. J Manag Care Pharm. 2011;17(7):531-46.	15.37	113.59
cost_DCC	Annual health state cost for decompensated cirrhosis (Adjusted to 2016 $)	20653.2502	15489.9376	25816.5627	Gamma (Mean = 0.012181108; SE = 0.003107062)	Davis KL, Mitra D, Medjedovic J, Beam C, Rustgi V. Direct economic burden of chronic hepatitis C virus in a United States managed care population. Journal of Clinical Gastroenterology. 2011;45(2):e17.; McAdam-Marx C, McGarry LJ, Hane CA, Biskupiak J, Deniz B, Brixner DI. All-cause and incremental per patient per year cost associated with chronic hepatitis C virus and associated liver complications in the United States: A managed care perspective. J Manag Care Pharm. 2011;17(7):531-46.	15.37	1261.79
cost_HCC	Annual health state cost for hepatocellular carcinoma (Adjusted to 2016 $)	37979.8667	28484.9	47474.8333	Gamma (Mean = 0.006624029; SE = 0.001689605)	Davis KL, Mitra D, Medjedovic J, Beam C, Rustgi V. Direct economic burden of chronic hepatitis C virus in a United States managed care population. Journal of Clinical Gastroenterology. 2011;45(2):e17.; McAdam-Marx C, McGarry LJ, Hane CA, Biskupiak J, Deniz B, Brixner DI. All-cause and incremental per patient per year cost associated with chronic hepatitis C virus and associated liver complications in the United States: A managed care perspective. J Manag Care Pharm. 2011;17(7):531-46.	15.37	2320.34
cost_LT	Annual health state cost for liver transplant (Adjusted to 2016 $)	109824.715	82368.5363	137280.894	Gamma (Mean = 0.00229276; SE = 0.000584819)	Davis KL, Mitra D, Medjedovic J, Beam C, Rustgi V. Direct economic burden of chronic hepatitis C virus in a United States managed care population. Journal of Clinical Gastroenterology. 2011;45(2):e17.; McAdam-Marx C, McGarry LJ, Hane CA, Biskupiak J, Deniz B, Brixner DI. All-cause and incremental per patient per year cost associated with chronic hepatitis C virus and associated liver complications in the United States: A managed care perspective. J Manag Care Pharm. 2011;17(7):531-46.	15.37	6703.71

Table A5: CEA Model Parameters (cont.)

Parameter Name	Description of Parameter	Base Case	Min	Max	Distribution	Reference
cost_F0_SVR	Annual health state cost for F0 after cure	.25 * cost_F0	-	-	-	Assumption (Hepatologist/Expert Opinion); These annual health state costs are linked to the annual health state costs above and so they are varied accordingly in the PSA simulations.
cost_F1_SVR	Annual health state cost for F1 after cure	.25 * cost_F1	-	-	-	Assumption (Hepatologist/Expert Opinion); These annual health state costs are linked to the annual health state costs above and so they are varied accordingly in the PSA simulations.
cost_F2_SVR	Annual health state cost for F2 after cure	.25 * cost_F2	-	-	-	Assumption (Hepatologist/Expert Opinion); These annual health state costs are linked to the annual health state costs above and so they are varied accordingly in the PSA simulations.
cost_F3_SVR	Annual health state cost for F3 after cure	.50 * cost_F3	-	-	-	Assumption (Hepatologist); These annual health state costs are linked to the annual health state costs above and so they are varied accordingly in the PSA simulations.
cost_F4_SVR	Annual health state cost for F4 after cure	.50 * cost_F4	-	-	-	Assumption (Hepatologist/Expert Opinion); These annual health state costs are linked to the annual health state costs above and so they are varied accordingly in the PSA simulations.
cost_DCC_SVR	Annual health state cost for decompensated cirrhosis after cure	.75 * cost_DCC	-	-	-	Assumption (Hepatologist/Expert Opinion); These annual health state costs are linked to the annual health state costs above and so they are varied accordingly in the PSA simulations.
cost_HCC_SVR	Annual health state cost for hepatocellular carcinoma after cure	.75 * cost_HCC	-	-	-	Assumption (Hepatologist/Expert Opinion); These annual health state costs are linked to the annual health state costs above and so they are varied accordingly in the PSA simulations.
cost_LT_SVR	Annual health state cost for liver transplant after cure	.75 * cost_LT	-	-	-	Assumption (Hepatologist/Expert Opinion); These annual health state costs are linked to the annual health state costs above and so they are varied accordingly in the PSA simulations.

Table A5: CEA Model Parameters (cont.)

Parameter Name	Description of Parameter	Base Case	Min	Max	Distribution	Reference
One Time costs Associated with Tx						
cost_adherence_monitor	One time cost of medication adherence monitoring	100	0	1000	Uniform	Assumption
cost_followuphcvrna	One time cost of the follow-up HCV RNA assessment	79	39	118	Uniform	Chahal et al: Rein DB, Wittenborn JS. The Cost-Effectiveness of Birth Cohort and Universal Hepatitis C Antibody Screening in U.S. Primary Care Settings - Technical Report. Research Triangle Park, NC: RTI International;2011.; 32. Carlson JJ, Kowdley KV, Sullivan SD, Ramsey SD, Veenstra DL. An evaluation of the potential costeffectiveness of non-invasive testing strategies in the diagnosis of significant liver fibrosis. Journal of gastroenterology and hepatology. May 2009;24(5):786-791.
cost_svr12	One time cost of assessing sustained virologic response at 12 weeks	26	13	39	Uniform	Chahal et al: Rein DB, Wittenborn JS. The Cost-Effectiveness of Birth Cohort and Universal Hepatitis C Antibody Screening in U.S. Primary Care Settings - Technical Report. Research Triangle Park, NC: RTI International;2011.; 32. Carlson JJ, Kowdley KV, Sullivan SD, Ramsey SD, Veenstra DL. An evaluation of the potential costeffectiveness of non-invasive testing strategies in the diagnosis of significant liver fibrosis. Journal of gastroenterology and hepatology. May 2009;24(5):786-791.
Annual cost after Tx completion if patient was cirrhotic						
cost_hccscreen	Annual cost of liver cancer screening	287	141	443	Uniform	Assumption: Includes an alphafetoprotein test and an ultrasound of liver (VCTE)

Table A5: CEA Model Parameters (cont.)

Parameter Name	Parameter Description	Base Case	Min	Max	Distribution	Reference
util_F0	health state utility for stage F0	0.85	0.83	0.87	Uniform	Thein HH, Krahn M, Kaldor JM, Dore GJ. Estimation of utilities for chronic hepatitis C from SF-36 scores. Am J Gastroenterol. Mar 2005;100(3):643-651.; HaganLM, SulkowskiMS, SchinaziRF. Cost analysis of sofosbuvir/ ribavirin versus sofosbuvir/simeprevir for genotype1 hepatitisC virus in interferon-ineligible/intolerant individuals .Hepatology2014;60:37–45.
util_F1	health state utility for stage F1	0.85	0.83	0.87	Uniform	Thein HH, Krahn M, Kaldor JM, Dore GJ. Estimation of utilities for chronic hepatitis C from SF-36 scores. Am J Gastroenterol. Mar 2005;100(3):643-651.; HaganLM, SulkowskiMS, SchinaziRF. Cost analysis of sofosbuvir/ ribavirin versus sofosbuvir/simeprevir for genotype1 hepatitisC virus in interferon-ineligible/intolerant individuals .Hepatology2014;60:37–45.
util_F2	health state utility for stage F2	0.85	0.83	0.87	Uniform	Thein HH, Krahn M, Kaldor JM, Dore GJ. Estimation of utilities for chronic hepatitis C from SF-36 scores. Am J Gastroenterol. Mar 2005;100(3):643-651.; HaganLM, SulkowskiMS, SchinaziRF. Cost analysis of sofosbuvir/ ribavirin versus sofosbuvir/simeprevir for genotype1 hepatitisC virus in interferon-ineligible/intolerant individuals .Hepatology2014;60:37–45.
util_F3	health state utility for stage F3	0.79	0.77	0.81	Uniform	Thein HH, Krahn M, Kaldor JM, Dore GJ. Estimation of utilities for chronic hepatitis C from SF-36 scores. Am J Gastroenterol. Mar 2005;100(3):643-651.; HaganLM, SulkowskiMS, SchinaziRF. Cost analysis of sofosbuvir/ ribavirin versus sofosbuvir/simeprevir for genotype1 hepatitisC virus in interferon-ineligible/intolerant individuals .Hepatology2014;60:37–45.
util_F4	health state utility for stage F4	0.76	0.67	0.79	Uniform	Thein HH, Krahn M, Kaldor JM, Dore GJ. Estimation of utilities for chronic hepatitis C from SF-36 scores. Am J Gastroenterol. Mar 2005;100(3):643-651.; HaganLM, SulkowskiMS, SchinaziRF. Cost analysis of sofosbuvir/ ribavirin versus sofosbuvir/simeprevir for genotype1 hepatitisC virus in interferon-ineligible/intolerant individuals .Hepatology2014;60:37–45.
util_DCC	health state utility for decompensated cirrhosis	0.69	0.44	0.69	Uniform	Coffin PO, Scott JD, Golden MR, Sullivan SD. Cost-effectiveness and population outcomes of general population screening for hepatitis C. Clinical infectious diseases : an official publication of the Infectious Diseases Society of America. 2012;54(9):1259-1271.
util_HCC	health state utility for hepatocellular carcinoma	0.67	0.6	0.72	Uniform	Coffin PO, Scott JD, Golden MR, Sullivan SD. Cost-effectiveness and population outcomes of general population screening for hepatitis C. Clinical infectious diseases : an official publication of the Infectious Diseases Society of America. 2012;54(9):1259-1271.
util_LT	health state utility for liver transplant	0.5	0.3	0.8	Uniform	Coffin PO, Scott JD, Golden MR, Sullivan SD. Cost-effectiveness and population outcomes of general population screening for hepatitis C. Clinical infectious diseases : an official publication of the Infectious Diseases Society of America. 2012;54(9):1259-1271.
util_LT_year2	health state utility for liver transplant in years after the initial liver transplant	0.67	0.57	0.77	Uniform	Coffin PO, Scott JD, Golden MR, Sullivan SD. Cost-effectiveness and population outcomes of general population screening for hepatitis C. Clinical infectious diseases : an official publication of the Infectious Diseases Society of America. 2012;54(9):1259-1271.

Table A5: CEA Model Parameters (cont.)

Parameter Name	Parameter Description	Base Case	Min	Max	Distribution	Reference
util_F0_SVR	health state utility for F0 after cure	1	0.98	1	Uniform	Liu S, Cipriano LE, Holodniy M, Owens DK, Goldhaber-Fiebert JD. New protease inhibitors for the treatment of chronic hepatitis C: a cost-effectiveness analysis. Annals of internal medicine. Feb 21 2012;156(4):279-290.
util_F1_SVR	health state utility for F1 after cure	1	0.98	1	Uniform	Liu S, Cipriano LE, Holodniy M, Owens DK, Goldhaber-Fiebert JD. New protease inhibitors for the treatment of chronic hepatitis C: a cost-effectiveness analysis. Annals of internal medicine. Feb 21 2012;156(4):279-290.
util_F2_SVR	health state utility for F2 after cure	0.933	0.92	1	Uniform	Liu S, Cipriano LE, Holodniy M, Owens DK, Goldhaber-Fiebert JD. New protease inhibitors for the treatment of chronic hepatitis C: a cost-effectiveness analysis. Annals of internal medicine. Feb 21 2012;156(4):279-290.
util_F3_SVR	health state utility for F3 after cure	0.86	0.82	0.9	Uniform	Liu S, Cipriano LE, Holodniy M, Owens DK, Goldhaber-Fiebert JD. New protease inhibitors for the treatment of chronic hepatitis C: a cost-effectiveness analysis. Annals of internal medicine. Feb 21 2012;156(4):279-290.
util_F4_SVR	health state utility for F4 after cure	0.83	0.79	0.87	Uniform	Liu S, Cipriano LE, Holodniy M, Owens DK, Goldhaber-Fiebert JD. New protease inhibitors for the treatment of chronic hepatitis C: a cost-effectiveness analysis. Annals of internal medicine. Feb 21 2012;156(4):279-290.
util_DCC_SVR	health state utility for DCC after cure	0.89	0.77	0.93	Uniform	Chhatwal, Jagpreet, et al. "Optimal Timing of Hepatitis C Treatment for Patients on the Liver Transplant Waiting List." Hepatology (2016). Print.
util_HCC_SVR	health state utility for HCC after cure	0.89	0.77	0.93	Uniform	Chhatwal, Jagpreet, et al. "Optimal Timing of Hepatitis C Treatment for Patients on the Liver Transplant Waiting List." Hepatology (2016). Print.
util_LT_SVR	health state utility for liver transplant after cure	0.89	0.77	0.93	Uniform	Chhatwal, Jagpreet, et al. "Optimal Timing of Hepatitis C Treatment for Patients on the Liver Transplant Waiting List." Hepatology (2016). Print.

Table A5: CEA Model Parameters

Parameter Name	Description of Parameter	Base Case	Min	Max	Distribution	Reference
ic_F0	**lost income in stage F0**	(1-util_F0) * median_inc	-	-	-	Assumption - these are all linked to the variable median_inc and vary with the variations in median_inc
ic_F1	**lost income in stage F1**	(1-util_F1) * median_inc	-	-	-	Assumption - these are all linked to the variable median_inc and vary with the variations in median_inc
ic_F2	**lost income in stage F2**	(1-util_F2) * median_inc	-	-	-	Assumption - these are all linked to the variable median_inc and vary with the variations in median_inc
ic_F3	**lost income in stage F3**	(1-util_F3) * median_inc	-	-	-	Assumption - these are all linked to the variable median_inc and vary with the variations in median_inc
ic_F4	**lost income in stage F4**	(1-util_F4) * median_inc	-	-	-	Assumption - these are all linked to the variable median_inc and vary with the variations in median_inc
ic_DCC	**lost income in decompensated cirrhosis**	(1-util_DCC) * median_inc	-	-	-	Assumption - these are all linked to the variable median_inc and vary with the variations in median_inc
ic_HCC	**lost income in hepatocellular carcinoma**	(1-util_HCC) * median_inc	-	-	-	Assumption - these are all linked to the variable median_inc and vary with the variations in median_inc
ic_LT	**lost income in liver transplant**	(1-util_LT) * median_inc	-	-	-	Assumption - these are all linked to the variable median_inc and vary with the variations in median_inc
median_inc	**median annual household income (national)**	$59,093	44319.8	73866.25	Uniform: +/- 25%	Kaiser State Facts Webpage/Assumption - base case is national annual median
cost_informalcare	**annual cost of informal caregiver time**	5166.29	3874.72	6457.8625	Uniform: +/- 25%	Bureau of Labor Statistics - Occupational Employment Statistics - Occupational Employment and Wages, May 2016 Home Health Aides (https://www.bls.gov/oes/current/oes311011.htm) - for health states F4 and above without cure

Table A5: CEA Model Parameters (cont.)

Parameter Name	Description of Parameter	Base Case	Min	Max	Distribution	Reference
cost_infcare_F0SVR	annual cost of informal caregiver time for F0 after cure	(cost_informalcare - (cost_informalcare*(util_F0_SVR - util_F0)))	-	-	-	Assumption - informal care in each of the states is linked to the difference between the health state utilities in F0 before and after cure; varies with the utilities and magnitude of informal care
cost_infcare_F1SVR	annual cost of informal caregiver time for F1 after cure	(cost_informalcare - (cost_informalcare*(util_F1_SVR - util_F1)))	-	-	-	Assumption - informal care in each of the states is linked to the difference between the health state utilities in F1 before and after cure; varies with the utilities and magnitude of informal care
cost_infcare_F2SVR	annual cost of informal caregiver time for F2 after cure	(cost_informalcare - (cost_informalcare*(util_F2_SVR - util_F2)))	-	-	-	Assumption - informal care in each of the states is linked to the difference between the health state utilities in F2 before and after cure; varies with the utilities and magnitude of informal care
cost_infcare_F3SVR	annual cost of informal caregiver time for F3 after cure	(cost_informalcare - (cost_informalcare*(util_F3_SVR - util_F3)))	-	-	-	Assumption - informal care in each of the states is linked to the difference between the health state utilities in F3 before and after cure; varies with the utilities and magnitude of informal care
cost_infcare_F4SVR	annual cost of informal caregiver time for F4 after cure	(cost_informalcare - (cost_informalcare*(util_F4_SVR - util_F4)))	-	-	-	Assumption - informal care in each of the states is linked to the difference between the health state utilities in F4 before and after cure; varies with the utilities and magnitude of informal care
cost_infcare_DCCSVR	annual cost of informal caregiver time for DCC after cure	(cost_informalcare - (cost_informalcare*(util_DCC_SVR - util_DCC)))	-	-	-	Assumption - informal care in each of the states is linked to the difference between the health state utilities in DCC before and after cure; varies with the utilities and magnitude of informal care
cost_infcare_HCCSVR	annual cost of informal caregiver time for HCC after cure	(cost_informalcare - (cost_informalcare*(util_HCC_SVR - util_HCC)))	-	-	-	Assumption - informal care in each of the states is linked to the difference between the health state utilities in HCC before and after cure; varies with the utilities and magnitude of informal care
cost_infcare_LTSVR	annual cost of informal caregiver time for LT after cure	(cost_informalcare - (cost_informalcare*(util_LT_SVR - util_LT)))	-	-	-	Assumption - informal care in each of the states is linked to the difference between the health state utilities in LT before and after cure; varies with the utilities and magnitude of informal care

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EDUCATION

Johns Hopkins Bloomberg School of Public Health
PhD Candidate in Health Economics
Department of Health Policy & Management GPA: 3.76/4.00 2018

Johns Hopkins Bloomberg School of Public Health
Certificate in Quality, Patient Safety and Outcomes Research
Department of Health Policy & Management 2014

Johns Hopkins Bloomberg School of Public Health
MHS in Health Economics
Department of Health Policy & Management GPA: 3.78/4.00 2013

New York University, *College of Arts and Sciences*
B.A. in Economics
Minor in French & Mathematics GPA: 3.43/4.00 2012

New York University in Paris, ***Paris, France*** 2010

RESEARCH EXPERIENCE

JHU Bloomberg School of Public Health
Research Assistant to Dr. Gerard Anderson (Baltimore, MD) *9/2015 – Present*
- Reducing U.S. Prescription Drug Spending in the Era of Specialty Drugs

JHSPH Center for Drug Safety and Effectiveness
Research Assistant to Dr. G. Caleb Alexander (Baltimore, MD) 5/2015 – 2/2016
- Use of Drug Coupons for Sofosbuvir Among the Commercially Insured

JHU School of Medicine, Division of Pulmonary and Critical Care Medicine 09/2014 – 09/2015
Site Preceptors: Dr. Dale Needham and Dr. A. Parker Ruhl
- Practicum Topic: Health Care Resource Use and Costs in ARDS Survivors: A One-Year Longitudinal National Multicenter Study

Hopkins Center for Health Disparities Solutions,
Research Assistant to Dr. Darrell Gaskin (Baltimore, MD) 6/2014 – 6/2017
- Examining Disparities in Costs and Treatment for Knee Osteoarthritis Using an Interactive Markov Model

John Hopkins Evidence-Based Practice Center
Research Assistant (Baltimore, MD) 12/2013 – 10/2014
- Public Reporting of Cost Measures in Health

JHU Bloomberg School of Public Health
Research Assistant to Dr. John Bridges (Baltimore, MD) 12/2012 – 1/2014
- Does Public Reporting Have An Impact on Healthcare Disparities? A Systematic Review

TEACHING EXPERIENCE

Teaching Assistant, Economic Evaluation I, JHSPH Fall 2015

- Graded assignments, CEA project, and final examination
- Answered student questions regarding concepts and application

Teaching Assistant, Public Health Economics Seminar, JHSPH 09/2014 – 05/2015
- Monitored online course website, attendance, and term assignments 09/2015 – 05/2016

Teaching Assistant, Introduction to the U.S. Healthcare System, JHSPH Fall 2013, 2014
- Graded both midterm and final exams and held office hours for students Spring 2015, 2016
- Monitored the online discussion forum

Teaching Assistant, Introduction to Health Economics, JHSPH Winter 2014, 2015, 2016
- Grading weekly assignments and final papers
- Answering questions and facilitating discussion amongst students on the online discussion board

PROFESSIONAL EXPERIENCE

Cost-Effectiveness Analysis Registry, Tufts Medical Center
*Article Reviewer (*Boston, MA) 07/2013 – 07/2016
- Reviewed cost-effectiveness analysis papers and abstracted CEA ratios and utility weights
- Conducted consensus meetings with other article reviewers to determine acceptance of article for registry

Mid-Atlantic Permanente Research Institute, KPMAS
Graduate Research Intern (Rockville, MD) *05/2016 - Present*
- Works with data analysts and research scientists to formulate research plans
- Conducts data analysis using claims and electronic health record data for specific projects

OTHER PROFESSIONAL ACTIVITIES

Member, *Academy Health* *2013 – Present*
Member, *International Society of Pharmacoeconomics and Outcomes Research (ISPOR)* *2015 – Present*
Member, *Society for Medical Decision Making (SMDM)* *2015 - Present*
Co-reviewer, *The New England Journal of Medicine***,** 2 Manuscripts

FUNDING SUPPORT

Predoctoral National Research Service Award Fellowship (T32)
Agency for Healthcare Research & Quality 09/2013 – 05/2015

Health Policy & Management Departmental Tuition Scholarship
Johns Hopkins 09/2015 – 08/2017

The Value of Novel Therapies for the Treatment of Hepatitis C in an Integrated Health Care System
- *Kaiser Permanente Mid-Atlantic States and Johns Hopkins Research Collaborative*
- *Principal Investigator:* W. Padula and C. Rodriguez
- *Grant Objective:* Develop Cost-effectiveness Model of Policies for the delivery and financing of Hepatitis C treatments
- *Role:* Co-Investigator, *Award:* $86,000 (50% FTE) *March 2016 - Present*

AWARDS & HONORS

Student Presentation Award 2016, Medical Care Section
American Public Health Association, Denver, CO 10/31/2016

Charles D. Flagle Scholarship Award 2017
Department of Health Policy & Management, JHSPH, Baltimore, MD 03/20/2017

LEADERSHIP

International Society for Pharmacoeconomics and Outcomes Research Student Chapter (JHSPH)
President-Elect *05/2016-03/2017*
President *03/2017 – Present*
Student Network Education Committee Chair *09/2017 - Present*

- Conduct and Preside over all meetings of ISPOR-SC
- Organize events for student member networking and career development

Student Coordinating Committee, Department of Health Policy & Management (JHSPH)
Co-Chair *9/2014 – 07/2015*

- Coordinated departments events with the fellow committee members
- Served as a liaison between students, faculty and staff to organize student forums with department chair

Wolfe Street Academy Tutoring
Tutor (Baltimore, MD) *10/2012 – 05/2013*

- Participated in one-on-one sessions each week with first grade student to develop reading, writing, and English speaking skills

PAPERS & PUBLICATIONS

Bridges JFP, Berger Z, Austin M, Nassery N, Sharma R, Chelladurai Y, **Karmarkar TD**, Segal JB. Public Reporting of Cost Measures in Health: An Environmental Scan of Current Practices and Assessment of Consumer Centeredness. Technical Brief No. 19 (Prepared by the Johns Hopkins University Evidence-based Practice Center under Contract No.290-2012-00007-I). AHRQ Publication No. 15-EHC009-EF. Rockville, MD: Agency for Healthcare Research and Quality. March 2015. www.effectivehealthcare.ahrq.gov/reports/final.cfm.

Karmarkar, T. D., Starner, C., Qiu, Y., Tiberg, K. and Gleason, P.P. "Sofosbuvir Initial Therapy Abandonment and Manufacturer Coupons in a Commercially Insured Population." *Am J Manag Care* 22.6 Spec No. (2016): Sp191-7.

Ruhl, A.P., Huang, M., Colantuoni, E., **Karmarkar T.,** Dinglas V.D., Hopkins R.O., Needham D.M. "Healthcare Utilization and Costs in ARDS Survivors: a 1-year longitudinal national US multicenter study." *Intensive Care Med* (2017) 43: 980.

Alexander, G.C., Ballreich, J., Socal, M.P., **Karmarkar, T.,** Trujillo, A., Greene, J., Sharfstein, J. and Anderson G. Reducing branded prescription drug prices: A review of policy options. *Pharmacotherapy*. Accepted Author Manuscript. doi:10.1002/phar.2013

Karmarkar, T.D., Maurer, A., Mason, T., Eastman, A., Harrington, M., Morgan, R., O'Connor, M., Wood, J. and Gaskin, DJ. "A Fresh Perspective on a Familiar Problem: Examining Disparities in Knee Osteoarthritis Using a Markov Model." *Med Care* (2017)

Ballreich, J., Alexander, C., Socal, M., **Karmarkar, T**., and Anderson, G. "Branded Prescription Drug Spending: A Framework to Evaluate Policy Options." *Journal of Pharmaceutical Policy and Practice (*2017) 10:31.

Mills, K., Greene, M., Dezube, R., Goodson, C., **Karmarkar, T.** and Pontone, G. "Efficacy and tolerability of antidepressants in Parkinson's Disease: A Systematic Review and Network Meta-Analysis." *Int J Geriatr Psychiatry (2017).*

WORKING PAPERS

Trujillo, A.J., **Karmarkar, T.,** Alexander, G.C., Padula, W., Greene, J., and Anderson, G. "Economists' view of Fairness in Drug Prices: Do they really think differently from the public?" *(Submitted for Publication)*

CONFERENCES & PRESENTATIONS

Posters:

Karmarkar, T., Bridges, J.F.P., and Berger, Z. "Does Public Reporting Have An Impact on Healthcare Disparities? A Systematic Review," 35th Annual North American Meeting for the Society for Medical Decision Making. Baltimore, MD, October 19-23, 2013.

Karmarkar, T., Maurer, A., Parks, M., Mason, T., Eastman, A., Harrington, M., Morgan, R., and Gaskin, D. J. "Examining Disparities in the Treatment and Costs of Knee Osteoarthritis Using an Interactive Markov Model." 37th Annual North American Meeting for the Society for Medical Decision Making. St. Louis, MO, October 19-21, 2015.

Karmarkar, T.D., Starner, C.I., Qiu, Y., Tiberg, K., Gleason, P.P. "Sofosbuvir Initial Medication Adherence and Prevalence of Copay Coupons Among the Commercially Insured." International Society for Pharmacoeconomics and Outcomes Research Annual International Meeting, Washington, D.C., May 21-25, 2016.

Karmarkar, T., Padula, W. V., Watson, E., Gaskin, D. J. and Rodriguez, C. V. "Factors Associated with Time-to-Treatment in the New Direct-Acting Antiviral Era for Hepatitis C Patients in an Integrated Health Care System." International Society for Pharmacoeconomics and Outcomes Research Annual International Meeting, Boston, MA, May 21-23, 2017.

Karmarkar, T., Rodriguez, C. V., Padula, W. V., Watson, E., and Gaskin, D. G. "Effect of Direct-Acting Antiviral Treatment for Chronic Hepatitis C on Post-Treatment Healthcare Resource Utilization." Society for Medical Decision Making, Pittsburgh, PA, October 23-24, 2017.

Presentations:

Karmarkar, T and Gaskin, D. J. "Musculoskeletal Health Disparities: An Economic Cost Model of Knee Arthritis." Movement is Life National Caucus on Arthritis & Musculoskeletal Health Disparities. Washington, D. C., November 13, 2014.

Karmarkar, T and Gaskin, D. J. "Innovative Patient Engagement and Decision Making Tool: Impact on Disparities." Movement is Life National Caucus on Arthritis & Musculoskeletal Health Disparities. Washington, D. C., November 12, 2015.

Karmarkar, T., Maurer, A., Parks, M., Mason, T., Eastman, A. Harrington, M., Morgan, R., O'Connor, M., Wood, J., and Gaskin, DJ. "A Fresh Perspective on a Familiar Problem: Examining Disparities in Knee Osteoarthritis Using a Markov Model." AcademyHealth Annual Research Meeting, Disparities Interest Group Meeting, Boston, MA, June 25, 2016.

Karmarkar, T. "A Fresh Perspective on a Familiar Problem: Examining Disparities in Knee Osteoarthritis Using a Markov Model." American Public Health Association Annual Meeting, Denver, CO, October 31, 2016.

Attended:

AcademyHealth Annual Research Meeting, Baltimore, MD, June 23-25, 2013.
AcademyHealth Annual Research Meeting, San Diego, CA, June 8-10, 2014.
ISPOR Annual International Meeting, Philadelphia, PA, May 18-20, 2015.
AcademyHealth Annual Research Meeting, Minneapolis, MN, June 14-16, 2015.
U.S. News & World Report – Hospital of Tomorrow Forum, Washington, D.C., October 18-20, 2015.

SKILLS & INTERESTS

Languages: English – Native; Marathi, Spoken – Fluent; French, Spoken – Beginner
Computer Applications: Proficient in Microsoft Office, Proficient in STATA, Experience in TREEAGE
Hobbies: Tennis, Cooking, Traveling
Strong interpersonal, communication and team skills